

Zero-case, is it the right national target for COVID-19 control activities?

Faris Al Lami¹

Many researchers believe that developing an effective vaccine may take years

A gradual building of herd immunity pose a more realistic approach.

While working hard to combat COVID-19, it seems that a lot of public health professionals in many countries are looking forward to have a zero-case status. Some professionals believe that resuming the normal or new normal activities are dependent on achieving the zero-case status, although, it is unknown how long this status will continue and whether new waves of the epidemic will be developed thereafter.

Considering the novelty of the virus and that, globally, no one had the specific immunity against it before its emergence, every individual around the globe should develop the immunity against this virus. This can be achieved either by contracting a natural infection or by vaccination against the new virus. The latter is still far, for at least the upcoming 12-18 months based on the most optimistic forecasting.¹ Many researchers believe that developing an effective vaccine is not guaranteed and the manufacturing of the vaccine may take years, based on previous experience with many vaccines like those for HIV, Malaria, Hepatitis C and others.²

Extensive efforts are made by many countries to achieve the zero-case status, and few have succeeded and reached this goal like Vietnam, New Zealand and others.^{3,4} Considering all the controversies demonstrated in the publications, the small number of people who contracted the infection had developed the necessary antibodies and hence the natural immunity against the disease, which is going to offer them protection against re-infection. How long will this immunity last? this is another question that is yet unsolved.⁵ But, what about the rest of the community who are indeed the bulk and who did not contract the infection and are left without a natural immunity? The only hope for this group to have the necessary immunity is to wait for the vaccine to be developed, manufactured and distributed.

Upon achieving the zero-case status, the countries have to keep their population fully secured against all potential sources of infection while waiting for the vaccine to be produced and become available for all. It necessitates keeping all the countries' doors and windows completely shut. These countries have to remain vigilant and to keep their population, the coming visitors, tourists, as well as the whole country's activities under strict and harsh supervision. It is evident that no herd immunity will be otherwise built.

All currently used basic public health practices to prevent contracting the disease (e.g. social distancing, using masks, hand hygiene... etc.) can greatly decrease but cannot completely prevent the spread of the disease. Based on this fact and lack of herd immunity, these populations will be exposed to successive epidemic waves upon any intrusion of the virus from whatever source and may necessitate partial or complete lockdown as a response.

Therefore, a gradual building of herd immunity through a partial slackening of lockdown, resumption of certain public and economic activities along with strict carrying out of basic public health practices (such as social distancing, hand hygiene, respiratory etiquette, using masks and others) pose a more realistic approach.

In reality, this can be the only available option for countries that cannot practically impose strict lockdown measures on the whole population, particularly, in countries with a large rural or suburban population, areas of security instability and populations of low socioeconomic status. This can also be the only available option for countries that cannot keep the economic activities, particularly tourism, closed for too long. Similarly, this option is also suitable for countries that do not have the capacity for achieving the highest level of a vigilant surveillance system (including lab capacity) available for a long time and to suffuse the entire countrywide area.

REFERENCES

1. Lanese N. When will a COVID-19 vaccine be ready? Retrieved from Livescience. (2020, April 16). Available at: <https://www.livescience.com/coronavirus-covid-19-vaccine-timeline.html>
2. AKPAN, N. (2020, April 10). Why a coronavirus vaccine could take way longer than a year. Retrieved from nationalgeographic: <https://www.nationalgeographic.com/science/2020/04/why-coronavirus-vaccine-could-take-way-longer-than-a-year/>
3. Worldmeter. (2020, May 9). COVID-19 CORONAVIRUS PANDEMIC. Retrieved from Worldmeter: <https://www.worldometers.info/coronavirus/#countries>.
4. Cousins S. New Zealand eliminates COVID-19. *The Lancet*, 2020;395(10235):1474.
5. Kikkert M. Innate Immune Evasion by Human Respiratory RNA Viruses. *Journal of Innate Immunity*, 2020;12(1):4–20.

Global preparedness for pandemics; COVID 19 the true and painful reality

Mohammed Al-Musawi¹

ABSTRACT

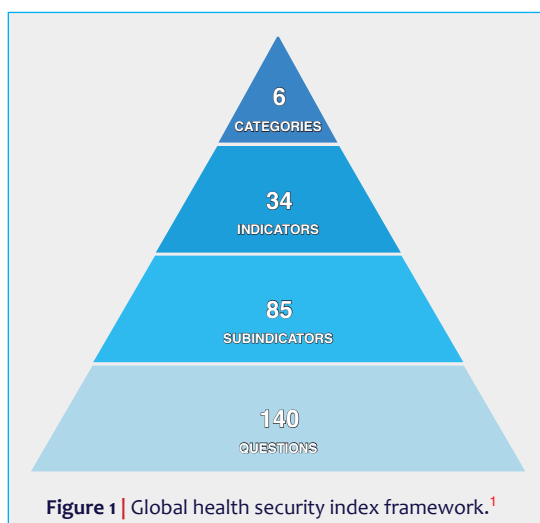
The world is facing a serious viral pandemic. A report was prepared and released only few months from the pandemic stated the global unpreparedness to face pandemics and biological crisis. Despite the relative better preparedness of few developed countries but this did not prevent the worse impact in them. The report quantitatively summarized the status among 195 country.

Key words: Global Health Security, GHS index, Pandemic, COVID-19.

In October 2019 Members of the Global Health Security (GHS) issued the Global Health Security (GHS) Index. The GHS Index is intended to be a key resource in the face of increasing risks of high-consequence and globally catastrophic biological events and considering major gaps in international financing for preparedness. The Global Health Security (GHS) Index is the first comprehensive assessment and of health security across 195 country . The West Africa Ebola epidemic crisis awakened the world to the reality that pathogens can emerge unexpectedly, and when outbreaks occur in countries that are unprepared, they can spill beyond borders, threatening the peace, health, and prosperity of all countries. However, despite newly available vaccines and therapies, response to the Ebola outbreak that began in 2018 in eastern Democratic Republic of Congo has been hampered by violence and instability, community resistance to outbreak mitigation measures, hospital transmission, delays in detection and isolation, and lack of funding and resources. Delays in the global response to Ebola in 2014 led to a restructuring of the WHO and prompted calls for measurement and transparent reporting of countries' public health capacities, including the launch of the voluntary WHO IHR Joint External Evaluations (JEEs). Since then, health, policy, and security leaders have developed numerous high-level reviews and recommended ways to identify, finance, and fill major

preparedness gaps. Nearly all recommendations pointed to a need to better understand and measure—on a transparent, global, and recurring basis—the state of international capability for preventing, detecting, and rapidly responding to epidemic and pandemic threats. An international advisory panel of 21 experts from 13 countries designed a detailed and comprehensive framework of 140 questions, organized across 6 categories, 34 indicators, and 85 sub indicators to assess a country's capability to prevent and mitigate epidemics and pandemics.

Let us see what was the striking conclusions of the report which came just before the



¹ MBCHB, MSc, FIBMS, FRCS. Consultant Cardiac surgeon, Research Faculty, Department of Surgery/ School of Medicine/University of Colorado, USA. Email address: mohammed.al-musawi@ucdenver.edu.

COVID 19 pandemic.

National health security is fundamentally weak around the world. No country is fully prepared for epidemics or pandemics, and every country has important gaps to address.

The GHS Index analysis finds no country is fully prepared for epidemics or pandemics. Collectively, international preparedness is weak. Many countries do not show evidence of the health security capacities and capabilities that are needed to prevent, detect, and respond to significant infectious disease outbreaks. The average overall GHS Index score among all 195 countries assessed is 40.2 of a possible score of 100. Among the 60 high-income countries, the average GHS Index score is 51.9. In addition, 116 high- and middle-income countries do not score above 50. Overall, the GHS Index finds severe weaknesses in country abilities to prevent, detect, and respond to health emergencies; severe gaps in health systems; vulnerabilities to political, socioeconomic, and

environmental risks that can confound outbreak preparedness and response; and a lack of adherence to international norms. Specific scores for the GHS Index categories are as follows:

PREVENTION: Fewer than 7% of countries score in the highest tier8 for the ability to prevent the emergence or release of pathogens.

DETECTION AND REPORTING: Only 19% of countries receive top marks for detection and reporting.

RAPID RESPONSE: Fewer than 5% of countries scored in the highest tier for their ability to rapidly respond to and mitigate the spread of an epidemic.

HEALTH SYSTEM: The average score for health system indicators is 26.4 of 100, making it the lowest-scoring category.

COMPLIANCE WITH INTERNATIONAL NORMS: Less than half of countries have sub-

Table 1 | Details of the score of Iraq for all six domains of global health Security Index model.¹ (Total index score is 25.8, the rank of Iraq is 167 out of 195).

	COUNTRY SCORE	AVERAGE SCORE*		COUNTRY SCORE	AVERAGE SCORE*
PREVENTION	22.1	34.8	HEALTH SYSTEM	11.8	26.4
Antimicrobial resistance (AMR)	8.3	42.4	Health capacity in clinics, hospitals and community care centers	5.6	24.4
Zoonotic disease	20.4	27.1	Medical countermeasures and personnel deployment	0	21.2
Biosecurity	0	16.0	Healthcare access	41.9	38.4
Biosafety	0	22.8	Communications with healthcare workers during a public health emergency	0	15.1
Dual-use research and culture of responsible science	0	1.7	Infection control practices and availability of equipment	0	20.8
Immunization	87.7	85.0	Capacity to test and approve new medical countermeasures	87.7	42.2
DETECTION AND REPORTING	42.2	41.9	COMPLIANCE WITH INTERNATIONAL NORMS	29.5	48.5
Laboratory systems	16.7	54.4	IHR reporting compliance and disaster risk reduction	50	62.3
Real-time surveillance and reporting	36.7	39.1	Cross-border agreements on public and animal health emergency response	0	54.4
Epidemiology workforce	25	42.3	International commitments	43.8	53.4
Data integration between human/ animal/environmental health sectors	100	29.7	JEE and PVS	0	17.7
RAPID RESPONSE	19.5	38.4	Financing	16.7	36.4
Emergency preparedness and response planning	0	16.9	Commitment to sharing of genetic & biological data & specimens	66.7	68.1
Exercising response plans	0	16.9	RISK ENVIRONMENT	29.2	55.0
Emergency response operation	0	23.6	Political and security risks	7.1	60.4
Linking public health and security authorities	0	22.6	Socio-economic resilience	53.6	66.1
Risk communication	0	39.4	Infrastructure adequacy	8.3	49.0
Access to communications infrastructure	68.4	72.7	Environmental risks	38.6	52.9
Trade and travel restrictions	100	97.4	Public health vulnerabilities	42.6	46.9

*Average: all 195 countries
Scores are normalized (0–100, where 100 = most favorable)

mitted Confidence-Building Measures under the Biological Weapons Convention (BWC) in the past three years, an indication of their ability to adhere to important international norms and commitments related to biological threats.

RISK ENVIRONMENT: Only 23% of countries score in the top tier for indicators related to their political system and government effectiveness.

The index score of Iraq is 25.8 and the rank is 167 out of 195 countries. **Table 1** represents the score of Iraq in the six categories.

Interestingly when they recently conducted countries vulnerability in the face of an outbreak like COVID-19, the country scores were analyzed against the total volume of domestic and international travelers per year, using flight data for all 195 countries and it showed that Americas and Asia are the most vulnerable.

Despite that the United States had a score 83.5 (out of a possible 100), the United States' response to the COVID-19 outbreak to date shows that capacity alone is insufficient if that capacity is not fully leveraged. Strong health systems must be in place to serve all populations, and effective political leadership that instills confidence in the government's response is crucial.

In the past four months, the world has seen how an isolated outbreak in one country has rapidly grown to a global pandemic. The COVID-19 outbreak has proven that a threat anywhere is a threat everywhere, and no country can rely on the strength of its own preparedness alone. The global average GHS Index score is just 40.2, and the response to the COVID-19 outbreak makes it clear that the world is collectively unprepared for a pandemic. Plans to combat COVID-19 require local, national, regional, and global action, and all countries has an obligation to address the gaps in its own system and to invest in countries that are far less prepared.

What is even more striking is that 9 out of 20 worse countries in term of COVID cases and death were from the best 20 countries in GHS Index. This raises many non-answered questions about the validity of the indicators. Also, it raised questions about how the prepar-

edness itself is not enough when the decision to act is in hands of politicians rather than in the hands of health policy makers. It raised questions about the impact an authoritarian government can have to manage the situation compared to democracies and what is the dividing line between what individual right is and what is public right. The pandemic revealed that even health issues are politicized nationally and internationally even in the worse global healthy situations.

CONCLUSION

The GHS Index which was adopted by UN showed the global no preparedness in the face of biological threats. It also raised many ethical issues about the difference between individual rights and public rights when governments need to stop spread of infections. And unfortunately, it showed how much the world is divided and had not cooperated to take joined preemptive measures to prevent such catastrophe. More collaboration and transparency between nations is required if we want to overcome the ongoing pandemic and to prevent future possible ones.

REFERENCES

1. Global Health Security Index, 2019. Available at: <https://www.ghsindex.org/wp-content/uploads/2019/10/2019-Global-Health-Security-Index.pdf>. Accessed on 1 May 2020.
2. Mao L, Wu X, Huang Z, Tatem AJ. Modeling monthly flows of global air travel passengers: An open-access data resource. *Journal of Transport Geography* 2015;48:52-60. Available at: <https://doi.org/10.1016/j.jtrangeo.2015.08.017>
3. NTI. The US and COVID-19: Leading the World by GHS Index Score, not by Response. April 21, 2020. Available at: <https://www.nti.org/analysis/atomic-pulse/us-and-covid-19-leading-world-ghs-index-score-not-response/>. Accessed on 20 April 2020.



Abbreviations list: Corona virus disease 2019 (COVID 19), Global Health Security (GHS), Gross Domestic product (GDP), International Health Regulations (IHR), Joint External Evaluations (JEEs), World Health Organization (WHO).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this article a part from self funding.

Crisis Nephrology; Challenges During the COVID-19 Pandemic

Ala Ali¹

ABSTRACT

Times of crisis unmask all features of the health system and challenge all efforts and morals of health care professionals. Over the last five months, the current COVID-19 pandemic highlighted all these things. Nephrology services have greatly affected during this crisis time. Many medical, logistic, financial, and ethical challenges are facing the whole nephrology human workforce and services. Here we are reflecting on these issues with possible great future consequences.

Key words: Crisis, Nephrology, Pandemic, COVID-19.

“ The darkest places in hell are reserved for those who maintain their neutrality in times of moral crisis.”

Dante Alighieri - Inferno

The basic nephrology knowledge had been dated a long time ago with records from Mesopotamia, ancient Egypt, Greece, and others.¹ Pandemics and catastrophe occurred at different points of time in different geographical areas and civilizations. Thus, renal insults and challenges to treating them run in parallel with these history-changing events. So, it's always a daring situation to treat renal patients at such difficult times of the history of humankind. These events included but not limited to the great cholera pandemic, world wars, major earthquakes, tuberculosis, HIV, SARS, Ebola, and the recent COVID-19 pandemic.

During all these major events, different forms of renal injuries emerged mostly acute kidney injury (AKI) with its serious consequences, urinary tract traumas, and renal parenchymal lesions secondary to infective origins.

The complex pathophysiology of renal diseases and the intricate relation with other organs during acute illnesses add more burden to the health care providers to offer the best renal and medical care. This is in addition to the altered body physiology in the milieu of uremic patients with multiple comorbidities, or

the immune suppression state in renal transplant recipients.

Clinical challenges

Acute kidney injury is a potentially preventable event. It usually occurs secondary to severe dehydration, rhabdomyolysis, and /or sepsis and cytokines release.^{2,3} In previous reports of SARS and MERS-CoV infections, AKI developed in 5% to 15% cases and carried a high (60%–90%) in-hospital mortality rate.² All efforts to provide sanitary water, correcting fluid status, and avoidance of nephrotoxic medications are mandatory.

Access to renal replacement therapy (RRT) is a critical issue in such difficult times. The decision to go for haemodialysis (HD), peritoneal dialysis (PD), or continuous renal replacement therapy (CRRT) depends on logistics and availability. High cut-off membranes may be preferable for CRRT which may add more cost. Sometimes the dialysis setup is unable to handle the load and resources may not be enough to provide HD or CRRT for all patients. Here, acute PD may be an option. Thus, the decision for the type of RRT should have a pragmatic approach.

Acute PD can maximize the provision of dialysis resources during the surge of cases. It will decrease the number of inserted dialysis catheters and the possible bloodstream infec-

tions. Another advantage is the ability to train non-nursing staff in the PD procedure, which is not technically challenging but requires strict sterile technique.⁴

During the 2009 H1N1, there were some reports about a direct viral cytopathic renal injury.⁵ SARS-CoV-2 has been isolated from the urine sample of an infected patient, suggesting the kidney as the target of this novel coronavirus.⁶ Viral RNA has been identified in kidney tissue and urine.⁷ In a Chinese report of 710 patients admitted for COVID-19, 44% had proteinuria and haematuria and 26.7% had haematuria on admission.⁸ A case of collapsing glomerulonephritis has reported with no evidence of renal inflammation but mostly a direct viral effect on podocytes.⁹ A postmortem renal biopsy showed direct parenchymal infection of tubular epithelial cells and podocytes with marked acute tubular injury and erythrocyte aggregation in such severe lethal COVID-19.¹⁰

No reports were focusing on the outcome after the crisis of non-dialyzed chronic kidney disease (CKD) patients. In such times, the risk of infection acquisition and increased cardiovascular risk is equally serious. This causes difficulties to maintain an appropriate diet and to obtain the medication, next to the stressful conditions in which these patients have to live. Therefore, pandemic certainly generates medical and therapeutic problems in CKD patients, even if they are not yet on dialysis.¹¹

The maintenance dialysis program is the most common chronic life-saving medical service around the world. The dialysis facilities are great places for the spread of an air-borne disease between the immune-compromised patients themselves and the dialysis staff. This is apparent in developing countries and conflict areas with crowded dialysis units, poor infection control, and limited personal protective equipment (PPE).

Dialysis access and its delivery would be seriously affected. Dialysis mandates large volumes of microbiologically pure, controlled water (500 ml/min of treatment; one hundred twenty l for four hours session). This can be an obstacle to performing adequate dialysis in the developing world, however, it's going to be a downside at explicit times even in developed countries.¹²

In-center HD faces another challenge which is the strict adoption of infection control procedures that involves the whole pathway from patient's transport to discharge from the HD unit.

The major issues for chronic PD patients are the provision of dialysis consumables and the deal with acute complications that bring patients for acute care. Volume management needs special attention and the use of more hypertonic solutions is better than an urgent switch to haemodialysis. Here exposure to excess glucose needs to not be overlooked.¹³

With distorted infrastructures and limited resources or diverted clinical skills, the creation of dialysis access or PD catheter insertion is another challenge that needs to be endorsed well.

During such crisis time, renal transplant programs would be ceased to the degree of total shutdown as in the current COVID-19 pandemic. The SARS-CoV-2 infection has a severe course in renal and other solid organ transplant recipients.¹⁴ While no cases of H5N1 have occurred in transplant patients, and none of the previous pandemics occurred in an era when transplantation and immune-suppressed patients were common, graft dysfunction reported and Kidney transplant recipients had more severe COVID-19 pneumonia than the general population.^{15,16}

For transplantation units, The risks include unhygienic conditions, risk of infections of immune-compromised patients. The provision of antirejection medication may be compromised with serious patients risks. The intensification of immune suppression for the management of acute graft dysfunction will add more complexity.

Donor testing with RT-PCR and bronchoalveolar lavage and CT scan would be needed. Still, we do not have data on the sensitivity of multiple RT-PCR tests or RT-PCR tests with bronchoalveolar lavage in asymptomatic individuals. This will increase the costs and efforts in addition to limiting resources for other priorities.¹⁷

Thus, considering transplantation during this pandemic is complex. It may be easy to defer non-urgent transplantation but the big ethical challenge is transplanting high immu-

nological risk patients.¹⁸

Both dialysis patients and transplant recipients may be 'super-spreaders' of infection during influenza, or other contagious respiratory virus pandemics. They may shed large amounts of virus for prolonged periods, resulting in spread to a greater number of contacts.^{19,20}

Nephropharmacology and drug dosing

This is another challenge while caring for COVID-19 patients. At this time, there is much uncertainty in treatment strategies. All the proposed medications have some crossing points with nephrology. There are variable reports about the drug side effects. The cardiac risk of hydroxychloroquine may limit its use in patients with CKD. Different therapies but mainly antiretroviral therapy can affect calcineurin inhibitors metabolism in transplant patients. The recently increasing interest in using remdesivir can be limited in patients with glomerular filtration rate below 30 ml/min. There are very limited data regarding the use of immunomodulators like tocilizumab and sarilumab in such patients.²¹ This is in addition to the possible roles of combined use of ACEI/ARBs and/or statins in patients with multiple comorbidities like renal patients.^{22,23}

Vaccination

The influenza vaccination rate among dialysis and wait-listed patients has declined in the past decade in different countries mostly due to non-adherence to standards and inadequate liaison with infectious disease departments.^{24,25} A stricter follow of vaccination standards should be adopted and checked regularly. Considering the immune dysfunction in CKD, ESRD, and transplant patients, the introduction and synthesis of vaccines to prevent another COVID-19 wave is another challenge. The vaccine should protect without risking renal patients' lives.

Logistic and Financial Problems

The term logistics refers to 'the procurement, maintenance, distribution, and replacement of personnel and material', to have 'the right measure, at the right place, at the right time'.²⁶

These problems include;

- Infrastructures and the need for rapidly establishing safe and accessible dialysis units, high dependency units, and medical words for care.
- Maintenance of easy access to dialysis, and provision of dialysis consumables, and pure water supply.
- The availability of well-trained human resources and their mobilization to areas of need without risking their lives. There would be high rates of worker absenteeism ceasing other services, like transportation and communications.¹⁵
- The strict adoption of infection control procedures and the provision of PPE.
- There is a possible risk of reducing dialysis frequency which will affect the clinical status of patients especially those with fluid overload.
- Acute care initiative will divert the care of nephrology and transplant outpatients with possible patients' risks.
- The need for governmental and financial support which may need to transfer budgets to the care of renal patients amid an increasing need for the whole health system to support. Testing materials and media should be available and labs should be ready and may run in multiple shifts. A continuous supply chain should be available.

Also, the psychological burden on patients and health care providers and the fear of transmitting infections in between during pandemics should add another challenge.

All the above-mentioned challenges will have great future consequences. The complexity of managing renal patients, the increasing need for technology, the stress and exhaustion of healthcare providers, and the fiscal crisis will affect the whole nephrology workforce. Nephrology is facing a critical problem with declining interest and expanding demands.²⁷

What to do?

Prepare

Preparedness means the state of readiness, especially for war²⁸. Such pandem-

ics is just like a war state. When compared to other medical disciplines, renal services should always have a plan for serious events, especially in developing countries to mitigate the serious consequences. The plan should include a clear description of leadership, locations, teams, personnel, resources, and finance. A crisis simulation training and scenario should be practiced. Prepare all dialysis units with strict infection control procedures and always check for them. Disaster preparedness activities lead to improvements in knowledge, skills, or attitude. There needs to be a wider focus on the whole health care team, including allied health professionals and support staff. Evaluation during real disasters and the use of validated competencies and tools to deliver and evaluate disaster preparedness will lead to the best preparedness and response.^{29,30,31}

Act

The plan should be implemented. Check all the available human resources and services. Regularly assess the status to update responses and resources allocation. Each unit should follow WHO core components for infection prevention and control in all settings.³² During pandemics, the first goal in HD units is to maximize social distancing. The second goal is the early detection of any infected patients.³³

Educate

Never forget to educate colleagues, medical staff, and patients about how to deal with such a difficult situation. Even, you may start informing the patients through letters, text messaging, and phone calls before going to the hospital about any risks and special care or changing management plans.

Reflect on action

During the pandemic aftermath, you should reflect to fill the gaps and be ready for any future events. Better pandemic response education and communication within hospitals and the whole system are mandatory.

In conclusion, pandemics represent a serious challenge to the nephrology practice. Adherence to the principles of crisis medicine, with a well-prepared team and plans, is vital. Assignment of resources, technology, and per-

sonnel is mandatory to minimize the extent of medical, logistic, and legal problems, and saving as many lives as possible. This always means making difficult clinical decisions with ethical challenges, but never to be neutral in such times.

REFERENCES

1. Tos SG. Hippocratic medicine, and nephrology. *Am J Nephrol* 1994; 14: 264–269.
2. Vallejos A. The role of Nephrology in the influenza A (H1N1) pandemic. Update. *Nefrología* (English Edition). 2009;29(6):576-81.
3. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney International*. 2020;97(5):829-38.
4. El Shamy O, Sharma S, Winston J, Uribarri J. Peritoneal Dialysis During the Coronavirus 2019 (COVID-19) Pandemic: Acute Inpatient and Maintenance Outpatient Experiences [published online ahead of print, 2020 Apr 23]. *Kidney Med*. 2020;10.1016/j.xkme.2020.04.001.
5. West SD, Brunskill NJ. Complications associated with influenza infection. *Postgrad Med J* 2002;78:107-8.
6. Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol*. 2004; 203: 622–630
7. Naicker S, Yang C-W, Hwang S-J, Liu B-C, Chen J-H, Jha V. The Novel Coronavirus 2019 epidemic and kidneys. *Kidney International*. 2020;97(5):824-8.
8. Cheng Y, Luo R, Wang K, et al. Kidney impairment is associated with in-hospital death of COVID-19 patients [e-pub ahead of print]. *medRxiv* 2020.02.18.20023242.
9. Kissling S, Rotman S, Gerber C, Halfon M, Lamoth F, Comte D, Lhopitallier L, Sadallah S, Fakhouri F, Collapsing glomerulopathy in a COVID-19 patient. *Kidney International* (2020), DOI: <https://doi.org/10.1016/j.kint.2020.04.006>.
10. Su H, Yang M, Wan C, Yi L-X, Tang F, Zhu H-Y, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney International*. Available at: <https://doi.org/10.1016/j.kint.2020.04.003>
11. Sever MS, Lameire N, Van Biesen W, Vanholder R. Disaster nephrology: a new concept for an old problem. *Clinical Kidney Journal*. 2015;8(3):300-9.
12. Piccoli G, Pacitti A, Mangiarotti G, Jeantet A, Mezza E, Segoloni GP, et al. Blade Runner, blackout and haemofiltration: dialysis in times of catastrophe. *Nephrology Dialysis Transplantation*. 2005;20(3):663-4.
13. Wilkie M, Davies S. Peritoneal Dialysis in the time of COVID-19. *Peritoneal Dialysis International*. Available at: <https://doi.org/10.1177/0896860820921657>.
14. Fernández-Ruiz M, Andrés A, Loinaz C, Delgado JF, López-Medrano F, San Juan R, et al. COVID-19 in solid organ transplant recipients: a single-center case series from Spain. *American Journal of Transplantation*. 16 April 2020. <https://doi.org/10.1111/ajt.15929>
15. Kumar D, Humar A. Pandemic Influenza and Its Implications for Transplantation. *American Journal of Transplantation*.

- 2006;6(7):1512-7.
16. Zhu L, Gong N, Liu B, et al. Coronavirus Disease 2019 Pneumonia in Immunosuppressed Renal Transplant Recipients: A Summary of 10 Confirmed Cases in Wuhan, China. [Published online ahead of print, 2020 Apr 18]. *Eur Urol*. 2020; Available at: [S0302-2838\(20\)30214-1](https://doi.org/10.1016/j.eururo.2020.03.039). doi: 10.1016/j.eururo.2020.03.039
 17. Martino F, Plebani M, Ronco C. Kidney transplant programs during the COVID-19 pandemic. *The Lancet Respiratory Medicine*. 2020;8(5):e39. doi:10.1016/S2213-2600(20)30182-X.
 18. Ho QY, Chung SJ, Gan VHL, Ng LG, Tan BH, and Kee TYS. High-Immunological Risk Living Donor Renal Transplant during the COVID-19 Outbreak: Uncertainties and Ethical Dilemmas. *Am J Transplant*. 2020. DOI:10.1111/ajt.15949
 19. Kumar D, Humar A. Emerging viral infections in transplant recipients. *Curr Opin Infect Dis* 2005;18: 337–341.
 20. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: Risk factors, mortality, and the effect of antiviral therapy. *Clin Infect Dis* 2004;39:1300–1306.
 21. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *New England Journal of Medicine*. 2020. DOI: 10.1056/NEJMoa2007016
 22. Meziyerh S, Zwart TC, van Etten RW, Janson JA, van Gelder T, Alwayn IP, de Fijter JW, Reinders ME, Moes DJA, and de Vries AP. Severe COVID-19 in a renal transplant recipient: A focus on pharmacokinetics. *Am J Transplant* 2020. Doi:10.1111/ajt.15943
 23. NIH COVID-19 Treatment Guidelines. Covid19treatment-guidelines.nih.gov. Site Updated: April 21, 2020. Available at: <https://www.covid19treatmentguidelines.nih.gov/>. Accessed on 30 April 2020.
 24. Schulte K, Schierke H, Tamayo M, Hager L, Engehausen R, Raspe M, et al. Strategies for Improving Influenza Vaccination Rates in Patients with Chronic Renal Disease. *Dtsch Arztebl International*. 2019;116(23-24):413-9.
 25. Lee DH, Boyle SM, Malat G, Sharma A, Bias T, Doyle AM. Low rates of vaccination in listed kidney transplant candidates. *Transplant Infectious Disease*. 2016;18(1):155-9.
 26. Sever MS, Vanholder R. Recommendations for the management of crush victims in mass disasters. *Nephrol Dial Transplant* 2012; 27(Suppl 1): i1–67.
 27. Lane CA, Brown MA. Nephrology: a specialty in need of resuscitation? *Kidney International* 2009; 76:594–596.
 28. "Preparedness." Merriam-Webster.com Dictionary, Merriam-Webster, <https://www.merriam-webster.com/dictionary/preparedness>. Accessed 29 Apr. 2020.
 29. Sever MS, Lameire N, Vanholder R. Renal disaster relief: from theory to practice. *Nephrol Dial Transplant* 2009; 24: 1730–1735
 30. Gowing JR, Walker KN, Elmer SL, Cummings EA. Disaster Preparedness among Health Professionals and Support Staff: What is Effective? An Integrative Literature Review. *Prehosp Disaster Med*. 2017;32(3):321-328. DOI:10.1017/S1049023X1700019X
 31. Phillips JP, Ragazzoni L, Burel WG, Burkle FM, Keim M. Report from the COVID-19 Virtual Summit, Disaster Experts Speak Out, March 31, 2020 [published online ahead of print, 2020 Apr 21]. *Prehosp Disaster Med*. 2020;1-22. DOI:10.1017/S1049023X20000552
 32. Storr J. Redefining infection prevention and control in the new era of quality universal health coverage. *Journal of Research in Nursing*. 2016;21:39.
 33. Meijers B, Messa P, Ronco C. Safeguarding the Maintenance Hemodialysis Patient Population during the Coronavirus Disease 19 Pandemic. *Blood Purification*. 2020. Available at: <https://doi.org/10.1159/000507537>



Abbreviations list: Acute kidney injury (AKI), Angiotensin converting enzyme inhibitor/ angiotensin receptor blockers (ACEI/ARBs), Chronic kidney disease (CKD), Continuous renal replacement therapy (CRRT), Corona virus disease- 2019 (COVID-19), Haemodialysis (HD), Human immunodeficiency virus (HIV), Middle East respiratory syndrome- corona virus (MERS-CoV), Millilitre per minute (ml/min), Peritoneal dialysis (PD), personal protective equipment (PPE), renal replacement therapy (RRT), Reverse transcriptase polymerase chain reaction (RT-PCR), Ribonucleic acid (RNA), Severe acute respiratory syndrome (SARS).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this study a part from self funding.

Epidemiological Characteristics of confirmed COVID-19 cases in Iraq, three months situation analysis

Riyadh A. Alhilfi¹, Yasir Y. Majeed², Ali K. Banoosh³, Safaa S. Ali⁴, Ban A. Shnan⁵, Ammar B. Muftin⁶

ABSTRACT

INTRODUCTION: COVID-19 is an emerging respiratory disease that was first reported in December 2019 in China and was then declared a public health emergency and subsequently a global pandemic. It is caused by a novel coronavirus that resembles the SARS CoV1 virus with some genetic differences.

OBJECTIVE: To show the clinical fate and epidemiology of the patients confirmed to have COVID-19 in Iraq for the three months from 24 February to 24 May 2020 and to compare our data to those of neighbour and other eastern Mediterranean countries.

METHODS: A cross sectional study was conducted to show the epidemiology of laboratory confirmed COVID-19 cases in Iraq from 24 February to 24 May 2020. All cases were diagnosed exclusively in governmental laboratories in Baghdad and other provinces by real time PCR. Incidence rate per 100,000 population, cure rate and case fatality rate were calculated and compared to that of other Eastern Mediterranean countries.

RESULTS: There were 4,469 laboratory confirmed COVID-19 cases by 24 May 2020 in Iraq which make an incidence of 11.13 per 100,000. Total recoveries were 2,738 (61%). Iraq was ranked the 12th among the EMRO countries in terms of confirmed COVID-19 cases. Males were 2,430 (54%) of the total cases, the highest case count was among the age group of 30-39 years (18.9 %), while the least percentage was among the 80 years and above age group (1%). Of the totally infected persons, 207 (4.6) were healthcare workers, and 187 (~ 90 %) of them were nurses and medical doctors.

CONCLUSION: after the first three months of pandemic of COVID-19, Iraq still in the middle rank among other Eastern Mediterranean countries in form of number of confirmed, cure and death rate. Baghdad, followed by Basra and Najaf have the highest rate of infection while Anbar and Ninawa are the least provinces affected.

Key words: COVID-19, Iraq, Epidemiology.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an emerging respiratory infectious disease. Reported initially as a cluster of pneumonia of unknown cause in Wuhan, China in late December 2019.^{1,2} Molecular analysis has shown that the culprit pathogen is a novel coronavirus, which was named initially 2019-nCoV.³ On 11 February 2020, the World Health Organization (WHO) officially named the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease coronavirus disease 2019 (COVID-19).⁴ The virus is distinct from

both SARS-CoV and MERS-CoV, yet closely related.⁵ It has been suggested that COVID-19 may be less severe than SARS and MERS. But, it is more contagious.⁶ The WHO declared the outbreak a Public Health Emergency of International Concern on 30 January 2020 and a pandemic on March 11, 2020.²

With the rapid and wide transportation, the disease had been spread all over the world within few weeks. The United Arab Emirates was the first Eastern Mediterranean country to detect COVID-19 in late January 2020 followed by Egypt and Iran. Progressively over

¹ MBCHB, PhD Public Health. Director General, Public Health Directorate, Ministry of Health, Baghdad, Iraq.

² MBCHB, HDCM/FE, FETP. Field epidemiologist, Public Health Directorate, Ministry of Health, Baghdad, Iraq.

³ MBCHB, MSc Community Medicine. Community physician, Saladdin Health Directorate/ Saladdin, Iraq.

⁴ MBCHB, HDCM/FE, FETP. Field epidemiologist. Karbala Health Directorate/ Karbala, Iraq.

⁵ BDS. FETP resident. Public Health Directorate, Ministry of Health, Baghdad, Iraq.

⁶ BVMS, FETP resident. Administrator of CDC programme, Al-Numan Teaching Hospital, Al-Rusafa Health Directorate, Baghdad.

Corresponding Author: Yasir Y. Majeed, Public Health Directorate, Ministry of Health, Baghdad, Iraq.

E mail: iraqi70@gmail.com.

the next few weeks, all east Mediterranean countries have registered their first cases. In Iraq, the first case of COVID-19 was reported on 24th of February 2020.⁷

COVID-19 is a highly contagious disease and each infected person could infect others⁸ either directly through inhalation of respiratory droplets of an infected person or indirectly through fomites in the immediate environment around the infected person.⁹ Unlike SARS-CoV, transmission of COVID-19 occur during the prodromal period when those infected are mildly ill, and carry on usual activities, which contributes to the wide spread of infection.¹⁰ Although the infected droplets can be transmitted over a range of about one meter, WHO continues to recommend airborne precautions for circumstances and settings in which aerosol generating procedures and support treatment are performed, according to risk assessment.¹¹

In a cohort of 32,583 patients in China, median age of infected people was 56.7 years. Women were slightly more affected than men. Elderly over 80 years had a higher risk of having severe or critical cases compared to young adult less than 20 years.¹ In another study from china that recruited 44,672 patients about 80 % of cases were mild, 15 % severe, and 5 % critical with a case fatality 2.3 %.¹² The presenting common symptoms include fever, dry cough, dyspnoea, chest pain, fatigue and myalgia.⁵ Gastrointestinal symptoms are rarely reported.¹³ Development of pneumonia with CT changes is difficult to be assessed in all patients with COVID-19, however, in hospitalized patients all of them had pneumonia with abnormal findings on chest computed tomography.¹³

Older age, smoking and underlying non-communicable diseases (NCDs), such as diabetes, hypertension, cardiac disease, chronic lung disease and cancer, have been reported as risk factors for severe disease and death.¹⁴

Since the detection of the first case of COVID-19 in Iraq on 24 February 2020, The Public Health Directorate has published many situation reports about the epidemiology of COVID-19 in Iraq. These reports have included an updated data about the confirmed, cured, active and died patients with some other demographic characteristics. In this study we are presenting the clinical fate of the pa-

tients confirmed to have COVID-19 in Iraq for the three months from 24 February to 24 May 2020 showing some demographic features and comparing our data to that reported in Eastern Mediterranean countries.

METHODS

Setting and Design: This cross-sectional description was based of the national registry of the confirmed COVID-19 at the Ministry of Health in Iraq. Registry data are gathered, unified and analysed centrally at the Public Health Directorate in Baghdad in collaboration with sections of the communicable diseases in Health Directorates of all Iraqi provinces including Kurdistan region. The study covered the period of three months from 24 February to 24 May 2020.

Ethical consideration: The use of these data was approved by the Public Health Directorate, in accordance with the regulations of Ministry of Health in Iraq.

Definition of the cases: Confirmed cases of the COVID-19 that are used in this registry, hence this analysis, are those who were tested positive using a real time PCR on a sample of nasopharyngeal and oropharyngeal swap. The laboratory tests were done exclusively at governmental laboratories in Baghdad and health directorates in Iraq. Laboratory devices and kits used for the diagnosis of COVID-19 were of variable markers and versions. In the first few weeks of the pandemic, the Ministry of Health in Iraq has adopted a passive surveillance system where tests were performed on those with a clinical history suggestive of COVID-19, a history of travel to highly endemic countries, or a history of contact with a confirmed case of COVID-19. However, when the tests became available on a wide scale, many health directorates started an active surveillance to detect the cases in the community especially the communities that reported more confirmed cases.

Variables of the study and definitions: the following demographic variables were used for sake of this analysis; age distributed in eight groups each of a decade, gender, and address per provinces. Job description was reported only for the confirmed cases of COVID-19 from

healthcare workers.

Active case: Any patient who was confirmed COVID-19 and persistently shows positive results by real time PCR by 24 May 2020 is considered active case.

Cure case: A COVID-19 confirmed patient is considered cured when he/she turns negative on PCR in two consecutive samples 24 hours apart.

Cure rate: is the total number of cured cases divided by the total number of confirmed cases as recorded on 24 May 2020 multiplied by 100.

Age specific case fatality: Total number of deaths over the total number of confirmed cases within the same age group.

Death Case: For surveillance purposes, WHO defines a death for COVID-19 as a death resulting from a clinically compatible disease in a probable or confirmed case of COVID-19, unless there is a clear alternative cause of death not related to COVID-19 (for example, trauma). There should not be a period of complete recovery between illness and death.¹⁵

Incidence rate: total number of confirmed cases/ 100,000 population for each province. The total population of each province was tak-

en from the Department of Statistics / Ministry of Health.

Iraqi data was compared with the data of other Eastern Mediterranean countries.¹⁶

Statistical analysis: data were shown by tables and graphs using Microsoft Excel software 2019.

RESULTS

In the first three months of the pandemic in Iraq since the first case of COVID-19 registered, 4,469 confirmed cases were reported, 160 patients have died and 2,738 patients have cured. The incidence rate is 11.13 / 100,000 population. **Table 1** shows the confirmed, active, cure and dead patients distributed over the Iraqi provinces.

Table 2 shows the profile of Iraq compared to that of Eastern Mediterranean countries. **Figure 1** shows the map chart of the epidemiology of COVID-19 of Iraqi provinces and the neighbour countries. **Figure 2** shows the effect of complete and partial curfews on the number of the confirmed cases.

Of the totally confirmed cases during the studied period, 2,430 (54 %) were males and 2,039 (46 %) were female. 845 patient (18.9 %) were from age group 30-39 years, other demographic data are shown in the **table 3**. Confirmed and cured cases of COVID-19 age 10 years and below is shown in **figure 3**.

The number of health care workers get infected in the three months from 24 February to 24 May 2020. **Figure 4** shows the infected HCW according to their job description.

DISCUSSION

The first case of COV-

Table 1 | COVID-19 cases and indicators by province in Iraq, 24 February – 24 May 2020

Province	Confirmed	Active	Death	Cure	Cure rate %	Incidence rate/100,000
Baghdad	2,233	1,195	97	941	42 %	26.09
Basra	747	151	18	578	77 %	24.39
Najaf	318	13	6	299	94 %	20.52
Muthanna	117	18	4	95	81 %	13.64
Erbil	242	30	1	211	87 %	12.39
Kerbala	153	27	8	118	77 %	11.92
Sulaymaniya	215	38	4	173	80 %	9.44
Missan	52	5	2	45	87 %	4.44
Thi-Qar	96	20	4	72	75 %	4.35
Kirkuk	72	11	2	59	82 %	4.28
Wassit	59	17	3	39	66 %	4.06
Diyala	45	19	5	21	47 %	2.61
Babylon	49	5	5	39	80 %	2.25
Dahuk	26	7	0	19	73 %	1.91
Diwaniya	15	3	1	11	73 %	1.1
Sala-Aldin	13	4	0	9	69 %	0.77
Ninewa	12	6	0	6	50 %	0.31
Anbar	5	2	0	3	60 %	0.27
Total Iraq	4469	1571	160	2738	61 %	11.13

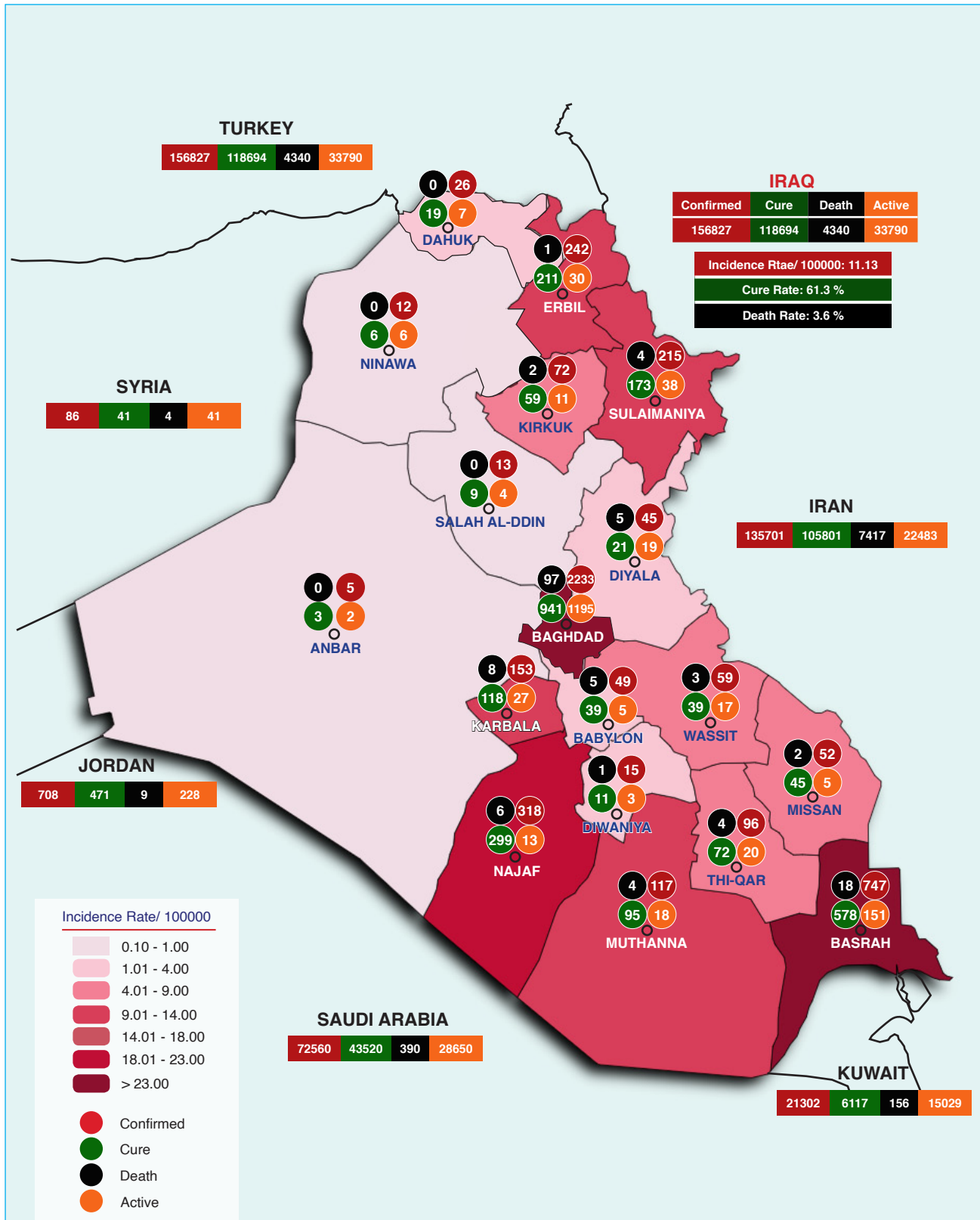


Figure 1 | Map chart shows confirmed, active, cure, and deaths of COVID-19 in Iraqi provinces up to 24 May 2020 (after 3 months from the first reported case) with a comparison with the registries of the neighbour countries.

Table 2 | COVID-19 case summary statistics in EMRO region till 24 May 2020

COUNTRY	CONFIRMED	DEATH	CURE	ACTIVE
Iran	135,701	7,417	105,801	22,483
Saudi Arabia	725,60	390	43,520	28,650
Pakistan	54,601	1,133	17,198	36,270
Qatar	43,714	23	9,170	34,521
UAE	29,485	245	15,056	14,184
Kuwait	21,302	156	6,117	15,029
Egypt	17,265	764	4,807	11,694
Afghanistan	10,582	218	1,075	9,289
Bahrain	9,138	13	4,587	4,538
Oman	7,770	37	1,933	5,800
Morocco	7,433	199	4,703	2,531
Iraq	4,469	160	2,738	1,571
Sudan	3,628	146	424	3,058
Djibouti	2,270	10	1,064	1,196
Somalia	1,594	61	204	1,329
Lebanon	1,114	26	688	400
Tunisia	1,048	48	914	86
Jordan	708	9	471	228
Palestine	423	3	357	63
Yemen	222	42	10	170
Syria	86	4	41	41
Libya	75	3	39	33
TOTAL	425,188	11,107	220,917	193,164

visited Iran.⁸ This study will have a look at the epidemiology of COVID-19 in Iraq after 3 months since the first recorded case.

The total confirmed COVID-19 cases in Iraq till 24 May 2020 were 4,469 with an incidence rate of 11.13/100,000 population. Of those 160 patients (3.6%) have died, 2,738 (61%) have been cured, and 1,571 (36.4%) continue as active cases. Iraq is the 12th in the ranking of total reported cases and 13th in the number of active cases among East Mediterranean countries. This rank is located in the middle where Iran is on its top and Libya is in its bottom.¹⁶ (see table 2) Rate of death in Iraq rank it the ninth, but it is the third among Arabic Asian countries after Yemen and Syria; however, it is much better compared to the world average, 6.3 %. While the cure rate puts Iraq within the first

ID-19 in Iraq was reported in Najaf province on 24 February; the patient was a theology student from Iran. Four more cases were reported in Kirkuk province on 25 February; the patients were an Iraqi family who recently returned from Iran. Two days later on, Baghdad announced its first confirmed case who had also recently

quarter.

Cure rate and case fatality rate in Iraq are much better than the average rates of the worlds which are 42 and 6.3 % respectively.¹⁶ However, it is important to note that the countries recorded numbers are dependent on the

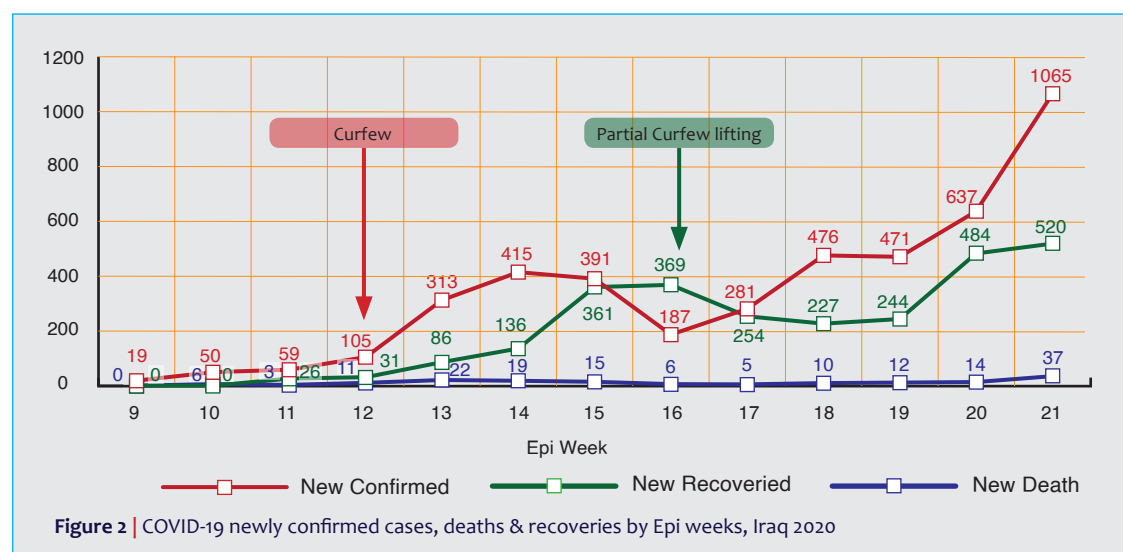
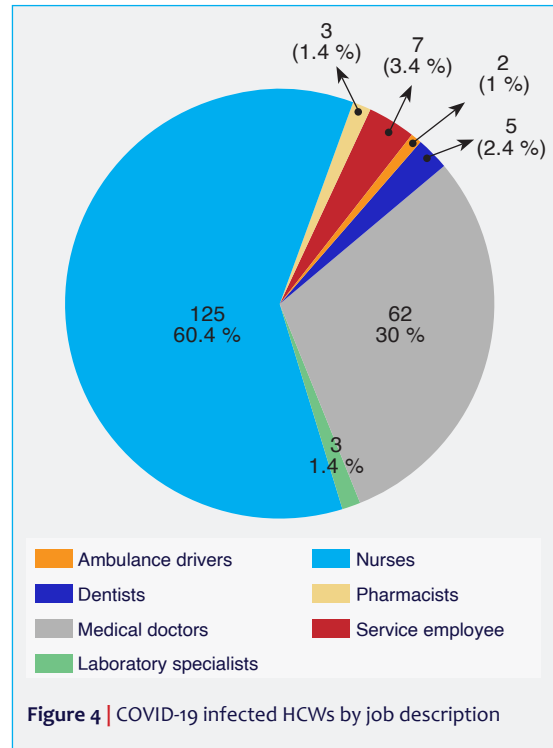


Table 3 | Epidemiological characteristics of COVID-19 cases in Iraq till 24 May 2020

Characteristic	Count	Percentage
Gender		
Male	2430	54
Female	2039	46
Age group (years)		
< 10	344*	7.7*
10-19	529	11.8
20-29	794	17.8
30-39	845	18.9
40-49	755	16.9
50-59	627	14.0
60-69	345	7.7
70-79	184	4.1
≥ 80	46	1.0
Travel history		
Yes	157	3.5
No	4299	96.2
Missing data	13	0.3

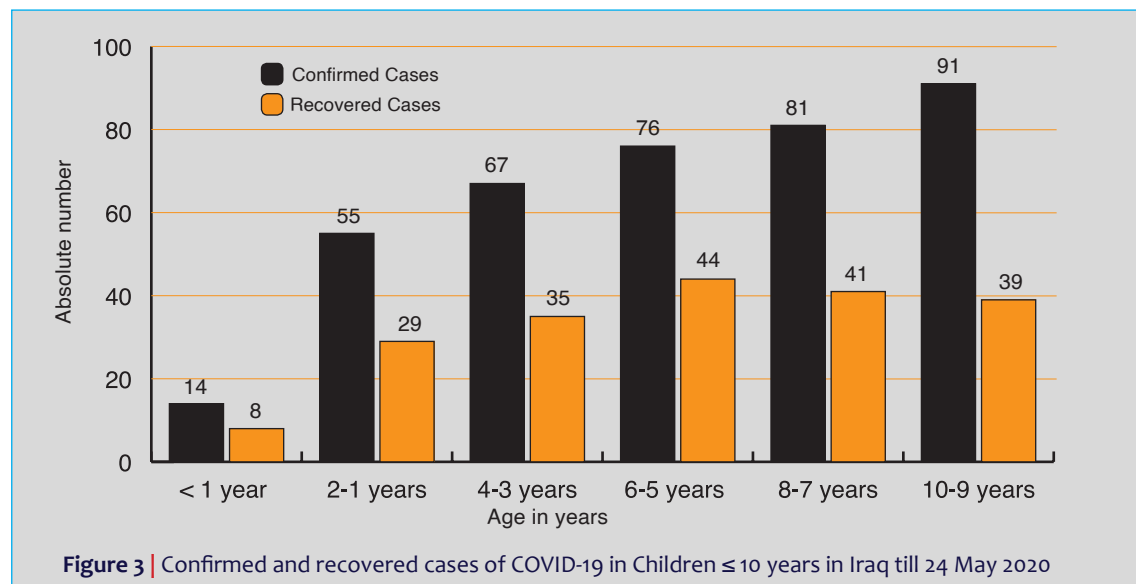
* This number and percent refers only to those below 10 years, In figure 3 and discussion section, 384 (8.6 %) refers to those aged 10 and below.



total number of testing conducted in each country and may not reflect the actual epidemiologic situation of COVID-19 burden. Globally, CFR is remarkably variable among different studies; it is around 2-3 % in overall patients,^{17,18} 11-15% in hospitalized patients^{13,19,20} and up 46 % among critically hospitalized patients.⁹

Table 1 shows the distribution of COVID-19 cases in Iraqi provinces, involvement of the provinces is diverse. Baghdad, Basra, and

Najaf have reported the highest incidence rate; 26.09, 24.39, and 20.52 cases/ 100,000 population respectively. All these provinces have shared the presence of an international airport; a state that makes the risk of importing infected cases higher. This notion is also applicable for Kurdistan region. While the incidence rate of COVID-19 in Erbil and Sulaymaniya, which have airports, are 12.39 and 9.44 per 100,000 population respectively, Dahuk, does



not have an airport, has an incidence rate of 1.9/ 100,000 population. The relation of risk of importing COVID-19 case with the presence of airports has been noted in China, India, and Africa.²¹

The total number of daily confirmed COVID-19 cases was increasing gradually as illustrated in **figure 2** till the 12th epiweek when complete curfew was implemented. Two weeks thereafter the number of confirmed cases started to decline coinciding with the maximum reported duration of action of the disease, which is 14 days.²² After changing the complete curfew to partial a second sharp rise in the confirmed cases has been noted.

In our study, males are slightly more affected by COVID-19 than females with a male:female ratio of 1.2:1. Many studies from Iran²³ and China^{24, 19} have shown similarly that males are more commonly affected than females. The more susceptibility to infection among men could be attributed to a more chance of men for contracting the infection because they relatively spend more time outside homes. Though some other opinions attributed this difference to the X chromosome and sex hormones, which have been reported to play role in innate and adaptive immunity²⁵ especially men are not only more infected than females but they are more serious and has a high mortality.^{23, 26}

Around 50 % of infected patients in this report are between age of 20-50 years (**see table 3**), then it progressively decreases with age reaching about 1 % in those over the age of 80 years. This is expected because adults are mainly involved in works outside homes exposing them to threat of having the infection. Besides that, people over the age of 65 years in Iraq comprises less than 5 % of the total Iraqi population.²⁷

In this report, 384 patients (8.6%) confirmed to have COVID-19 were aged 10 years and below. **Figure 3** shows that in this age group the recovered cases is usually more than the active cases, and the rate of confirmed cases is directly related to the age. Early reports from China has shown that infection of COVID-19 below age of 10 years is very rare; about 0.9%.²⁸ However, this low rate of infection of children does not necessarily reflect low susceptibility but due to less exposure in the first

days of the pandemic because children have fewer outdoor activities and undertake less international travel, making them less likely to contract the virus.²⁸ A systematic review showed that children have so far accounted for 1%-5% of diagnosed COVID-19 cases, they often have milder disease than adults and deaths have been extremely rare.²⁹

In Iraq, 207 health care workers (HCW) (4.6 %) have been infected with COVID-19 in the first three months (**See Figure 4**); nursing staff were 125 (60.4 %) and medical doctors were 62 (30%). COVID-19 is imposing a significant burden on HCW exposing them to a huge danger despite the availability of personal protective equipment. This is a worldwide problem, in Italy by 16 April 2020, 16,991 healthcare workers had tested positive for COVID-19. They represented about 10 % of the total infected people, of them 206 (1.2 %) have died.³⁰ Based on data from 30 countries, the international council of nursing has estimated that 90,000 healthcare workers have been infected on average of 6 % of all confirmed cases of COVID-19.³¹ High rate of involvement of HCW has raised a call to exercise more strict infection control programs and provision of effective personal protective equipment on a wide scale to protect the essential fighters of this dreadful enemy.

CONCLUSION

The review of Iraq data of COVID-19 pandemic has shown that it is in the middle rank compared to other countries of Eastern Mediterranean Region. Male are more affected than female and young adults are the highest age group to be involved.

REFERENCES

1. Pan A, Liu L, Wang C, et al. Association of Public Health Interventions with the Epidemiology of the COVID-19 Outbreak in Wuhan, China. *JAMA*. 2020;323(19):1915–1923. doi:10.1001/jama.2020.6130
2. WHO. Event as they happen 2020. Updated 1 June 2020. Available from: [novel-coronavirus-2019/events-as-they-happen](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen). <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>.
3. Sun J, He W-T, Wang L, Lai A, Ji X, Zhai X, et al. COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives. *Trends in Molecular Medicine*, May 2020;26(5):483-

- 495.
4. WHO. 2020. Naming the coronavirus disease (COVID-19) and the virus that causes it. Available from: [https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-\(covid-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it).
 5. Zhu N, Zhang D, Wang W, Li XW, Yang B, Song JD, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020 Feb 20;382(8):727-733. doi: 10.1056/NEJMoa2001017
 6. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395(10223):470-473. doi:10.1016/S0140-6736(20)30185-9.
 7. Ravelo JL, Jerving A. COVID-19: a timeline of the coronavirus outbreak. 2020 [updated on 30 May 2020; cited on 30 May 2020]. Available from: <https://www.devex.com/news/covid-19-a-timeline-of-the-coronavirus-outbreak-96396>.
 8. Alimohamadi Y, Taghdir M, Sepandi M. The Estimate of the Basic Reproduction Number for Novel Coronavirus disease (COVID-19): A Systematic Review and Meta-Analysis. *Journal of Preventive Medicine Public Health*. 2020; 53(3): 151-157. DOI: <https://doi.org/10.3961/jpmph.20.076>
 9. Ong SW, Tan YK, Chia PY, Lee TH, Ng OT, Wong MS, et al. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. *JAMA*. 2020;323(16):1610-1612. doi:10.1001/jama.2020.3227
 10. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci. China Life Sci*. 2020; 63:706-711. <https://doi.org/10.1007/s11427-020-1661-4>
 11. WHO. Infection Prevention and Control Guidance for COVID-19. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/infection-prevention-and-control>.
 12. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19)—China, 2020. *China CDC Weekly*, 2020;2(8):113-122. doi: 10.46234/ccdcw2020.032
 13. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;(395):497-506.
 14. WHO. Clinical management of COVID-19: interim guidance 27 May 2020. [Mar;2020]. Available from: [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected)
 15. WHO. International Guidelines For Certification and Classification (Coding) of COVID-19 as Cause Of Death. 16 April 2020. Available from: https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19.pdf
 16. Worldmeters. CoVID-19 Coronavirus Pandemic. Available from: <https://www.worldometers.info/coronavirus/>. Access May 30,2020.
 17. Zhao X, Zhang B, Li P, Ma C, Gu J, Hou P. Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis. medRxiv. 2020. Available from: <https://www.medrxiv.org/content/10.1101/2020.03.17.20037572v1>
 18. Wu Z, McGoogan J.M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Jama*. 2020.
 19. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;(395):507-513.
 20. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. *Travel medicine and infectious disease*, 2020; 34: 101623.
 21. Daon Y, Thompson RN, Obolski U. Estimating COVID-19 outbreak risk through air travel. medRxiv April 20,2020. doi: <https://doi.org/10.1101/2020.04.16.20067496>
 22. Lauer SA, Grantz KH, Qifang Bi, Jones FK, Zheng Q, Meredith HR, et al, LAUER, Stephen A., et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Annals of internal medicine*, 2020;1729(9):577-582. doi. [org/10.7326/M20-0504](https://doi.org/10.7326/M20-0504)
 23. Nikpouraghdam M, Jalali Farahani A, Alishiri G, et al. Epidemiological characteristics of coronavirus disease 2019 (COVID-19) patients in IRAN: A single center study. *J Clin Virol*. 2020;127:104378. doi:10.1016/j.jcv.2020.104378
 24. Guan WJ, Ni ZY, Yi Hu et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382: 1708-20. Available from: <https://doi.org/10.1056/NEJMoa2002032>
 25. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. *Clinical reviews in allergy & immunology*. 2019 Jun;56(3):308-321. doi: 10.1007/s12016-017-8648-x 1-14.
 26. Jin JM, Bai P, He W, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Health*. 2020;8:152. doi:10.3389/fpubh.2020.00152
 27. Central Statistical Organization/ Iraq. Demographic indicators. Available from: <http://cosit.gov.iq/ar/2013-01-31-08-43-38>
 28. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? *J Microbiol Immunol Infect*. 2020;53(3):371-372. doi:10.1016/j.jmii.2020.02.011
 29. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatrica*. 2020;109:1088-1095. Available from: <https://doi.org/10.1111/apa.15270>
 30. COVID-19 integrated surveillance: key national data. COVID-19 epidemic. 16 April 2020 national update. (In Italian). Italian National Institute of Health (ISS) website. Available from: <https://www.epicentro.iss.it/coronavirus/sars-cov-2-sorveglianza-dati>. [Published April 16, 2020. Accessed April 17, 2020].
 31. International council of Nursing. ICN calls for data on health-care worker infection rates and deaths. 6 May 2020. Available from: <https://www.icn.ch/news/icn-calls-data-healthcare-worker-infection-rates-and-deaths>. Accessed on 30 May 2020.



Abbreviations list: Case fatality rate (CFR), Coronavirus disease 2019 (COVID-19), Health care workers (HCW), Middle east respiratory syndrome corona virus (MERS-CoV), Noncommunicable diseases (NCDs), Polymerase chain reaction (PCR), Severe acute respiratory syndrome corona virus (SARS-CoV), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), World Health Organization (WHO).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this study a part from self funding.

Death from COVID-19 in Iraq, and its associated risk factor: a three-month situation analysis

Riyadh A. Alhilfi¹, Yasir Y. Majeed², Ali K. Banoosh³, Safaa S. Ali⁴, Ban A. Shnan⁵, Ammar B. Muftin⁶

ABSTRACT

INTRODUCTION: COVID-19 has distributed all over the world. The disease has a diverse clinical presentation ranging from mild to critical with few deaths. Elderly, men, and those with immunocompromised state or associated comorbidities are prone to have more severe symptoms and associated with higher risk of death.

OBJECTIVE: To present the case fatality rate of COVID-19 in Iraq and in each Iraqi province registered from 24 February to 24 May 2020 and to find an association between age, gender, and some comorbidities on death from COVID-19.

METHODS: A cross sectional study was conducted to show the epidemiology of cases died of COVID-19 which were diagnosed by RT PCR and registered at the National Registry of the Public Health Directorate, Ministry of Health in Iraq during the first three months of pandemic. We calculated the case fatality rate of each Iraqi province. Then we studied an association between death and age, gender, having coronary artery disease, hypertension, diabetes mellitus, cancer, chronic respiratory disease, and travel history.

RESULTS: Out of 4469 confirmed cases with COVID-19, 160 have died with a case fatality rate of 3.6 %. Diyala and Babylon were recorded the highest CFR; 5/45 (11.1 %) and 5/49 (10.2 %) respectively. Mean age in years, gender, having coronary artery disease, hypertension, diabetes mellitus, cancer, chronic respiratory disease were statistically associated with death from COVID-19, while travel history did not.

CONCLUSION: CFR of COVID in Iraq is in the middle rank compared to the neighbour countries and about half of the average of the world. Being a male, elderly, and having a chronic medical illness is statistically associated with death.

Key words: COVID-19, Iraq, case fatality rate.

INTRODUCTION

In December 2019, a cluster of pneumonia of unknown aetiology appeared in Wuhan City, in Hubei Province, China. Several of the initial patients visited a wet seafood market where other wildlife species were also sold.¹ The virus, which is called SARS-CoV-2 is an RNA virus of subgenus Sarbecovirus and of the genus Betacoronavirus, 60-140 nm in size, and has about 80 % similarity to severe acute respiratory syndrome.²

Although the outbreak is likely to have started from a zoonotic transmission, it soon became clear that efficient person-to-person transmission was also occurring.³ Trans-

mission of infectious diseases must rely on sources of infection, routes of transmission, and susceptibility of hosts.⁴ Transmission of COVID-19 is through respiratory droplets either directly or indirectly as it is in SARS-CoV, MERS-CoV, and highly pathogenic influenza.⁵ Duration of incubation period of an infectious disease and ways of transmission is important to determine the type and the duration of isolation and physical distancing. For COVID-19 incubation period is on average 5-6 days, however can be up to 14 days.^{6,7}

Patients with COVID-19 vary from being asymptomatic to respiratory failure due to acute respiratory distress syndrome. Fever,

¹ MBCHB, PhD Public Health. Director General, Public Health Directorate, Ministry of Health, Baghdad, Iraq.

² MBCHB, HDCM/FE, FETP. Field epidemiologist, Public Health Directorate, Ministry of Health, Baghdad, Iraq.

³ MBCHB, MSc Community Medicine. Community physician, Saladdin Health Directorate/ Saladdin, Iraq.

⁴ MBCHB, HDCM/FE, FETP. Field epidemiologist. Karbala Health Directorate/ Karbala, Iraq.

⁵ BDS. FETP resident. Public Health Directorate, Ministry of Health, Baghdad, Iraq.

⁶ BVMS, FETP resident. Administrator of CDC programme, Al-Numan Teaching Hospital, Al-Rusafa Health Directorate, Baghdad.

Corresponding Author: Yasir Y. Majeed, Public Health Directorate, Ministry of Health, Baghdad, Iraq., Baghdad, Iraq.

E mail: iraqi70@gmail.com.

cough, and dyspnea is the commonest presenting signs and symptoms.⁸

Although the vast majority of patients with COVID-19 cure completely, a few have died. Case fatality ratio (CFR), which is the proportion of those died from the disease to the all (asymptomatic and symptomatic) infected cases is the tool used to measure the mortality of a disease.⁹

The world case fatality is 5.9 %, but this figure differs among different countries; the highest rate is in France 15.2%, Italy 14.3%, and UK at 14.1%.¹⁰ Excess deaths from the COVID-19 pandemic might arise both in those infected (direct effects), as well as those affected (indirectly, not infected) by altered access to health care services; the physical, psychological, and social effects of distancing; and economic changes.¹¹

Older age, cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer were all associated with an increased risk of death.¹²

Gender plays a role in acquiring infection and its mortality. Males are affected more than female also case fatality in male is higher than female. Females contain more antibodies as compared which comparatively boost their immune system relative to the male. Again, females possess oestrogen as sex hormone, which gives them an upper hand than male. Studies suggest that oestrogen acts as a shield against lots of viral infections. In another study, females also own two X chromosomes. Consequently, they attain an extra copy of gene so as to elevate the immune system.¹³

In this report and based on the National Registry of COVID-19 of Ministry of Health in Iraq, we are reporting the case fatality rate of COVID-19 in Iraq and in each province registered during the first three months of the pandemic in Iraq; from 24 February to 24 May 2020. We also compare our data to that of other Eastern Mediterranean countries. And to find any association between mortality and age, gender, and some chronic comorbidities.

METHODS

Setting and Design: This cross-sectional

study was based on the national registry of confirmed COVID-19 cases at Ministry of Health in Iraq. The data of the registry is gathered, unified, and analysed centrally at the Public Health Directorate in Baghdad in collaboration with sections of communicable diseases control in Health Directorates of all Iraqi Provinces. The study covered the period of the first three months of pandemic from 24 February to 24 May 2020.

Ethical consideration: The use of this data was approved by the Public Health Directorate, in accordance with the regulations of the Ministry of Health in Iraq.

Definition of the cases: Confirmed cases of COVID-19 is any person tested positive by a real time PCR on a nasopharyngeal and/or oropharyngeal swab exclusively in governmental laboratories in Baghdad and other health directorates. Devices and kits for COVID-19 diagnosis that have been used were of varying makers and versions.

Variables of the study: we are reporting the confirmed cases, number of cases cured and number of cases died. CFR for each province and for Iraq in general was calculated. Age, gender, travel history, and presence of coronary artery disease (CAD), hypertension, diabetes mellitus, cancer, chronic respiratory disease were reported and their association to the mortality were tested. For the sake of this study we define:

Active case: Any patient who was confirmed COVID-19 and persistently shows positive results by real time PCR by 24 May 2020.

Cure case: A confirmed Patient with COVID-19 is considered cured when he/she turns negative on the PCR in two consecutive tests done 24 hours apart.

Cure rate: is the total number of cure cases divided by the total number of confirmed cases as recorded on 24 May 2020.

Age specific case fatality: Total number of deaths over the total number of confirmed cases within the same age group.

Death Case: For surveillance purposes, we used the WHO definition of death for COVID-19 “a death resulting from a clinically compatible disease in a probable or confirmed case of COVID-19, unless there is a clear alternative

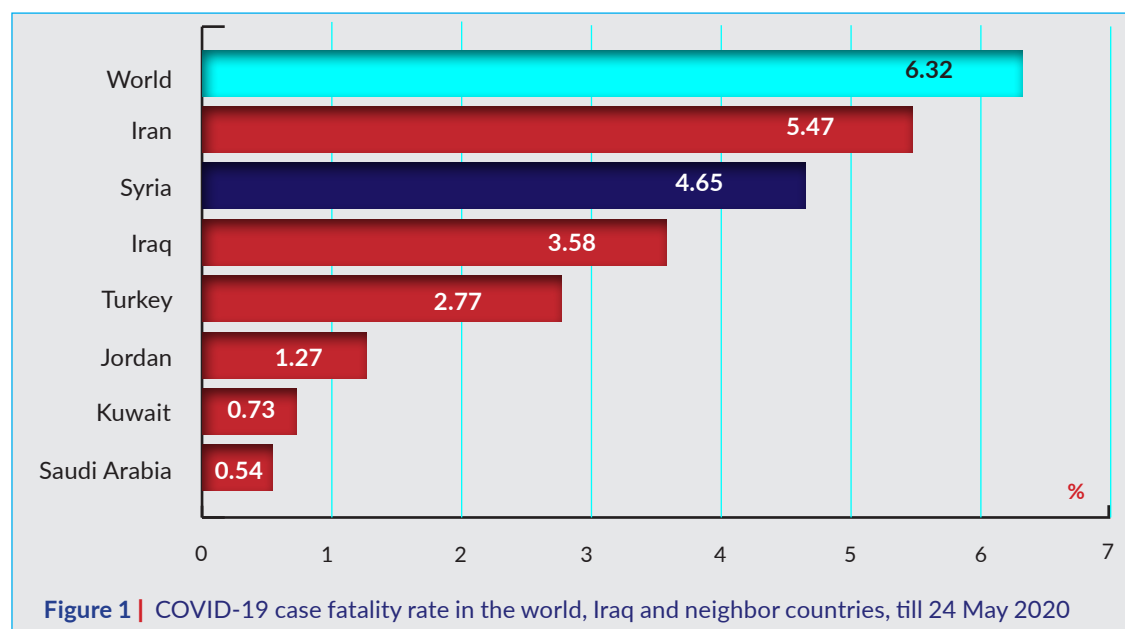
Table 1 | COVID-19 cases and indicators by province in Iraq, 24 February – 24 May 2020

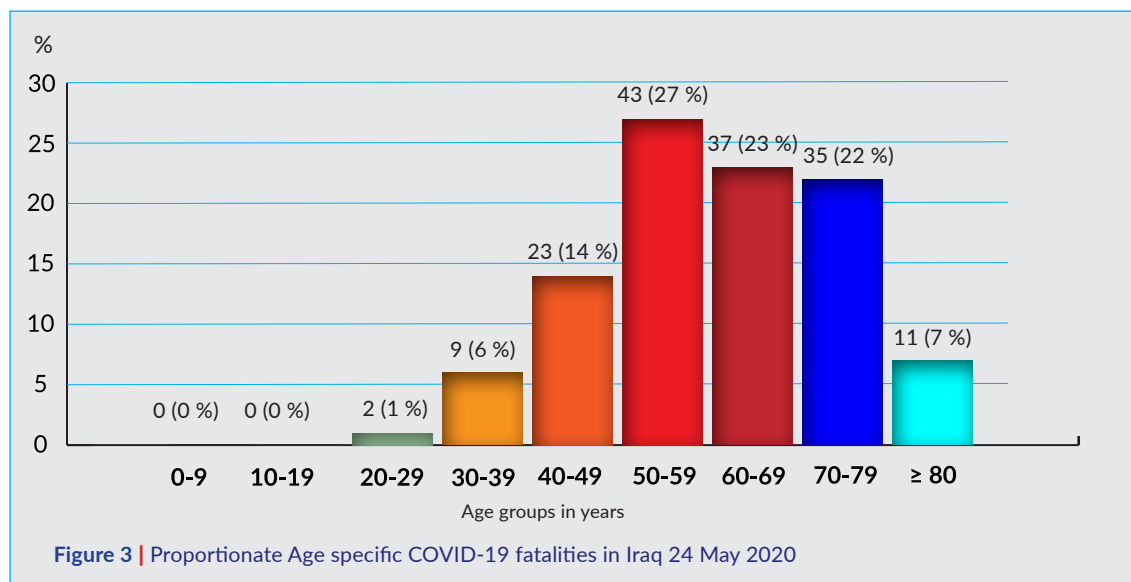
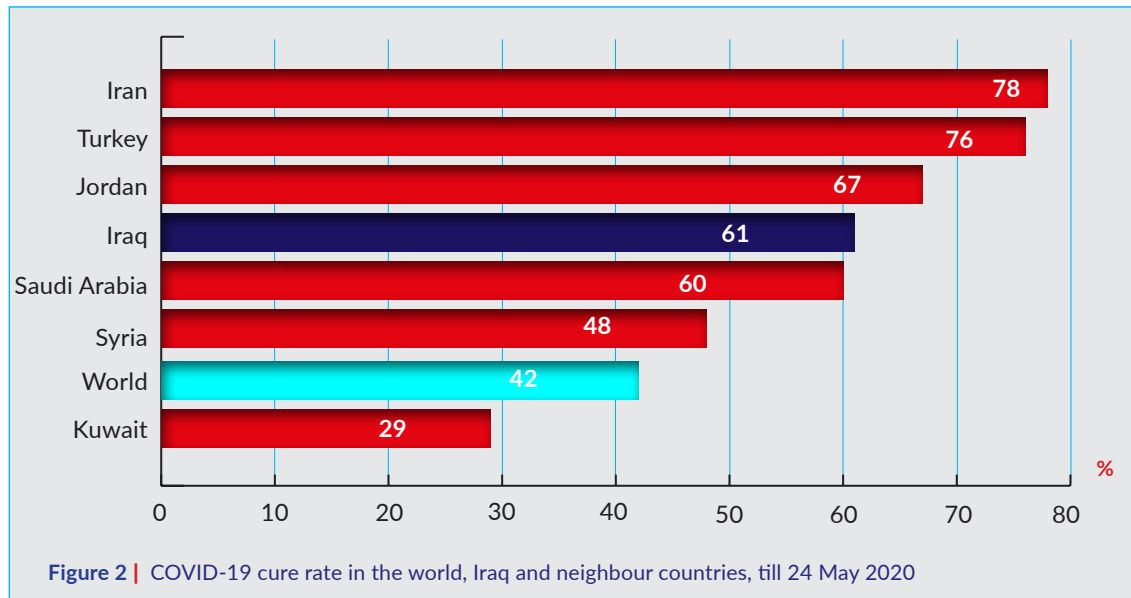
Province	Confirmed	Active	Death	Cure	CFR %	Cure rate %	Population	Incidence rate/100,000
Baghdad	2,233	1,195	97	941	4.3 %	42%	8,558,625	26.09
Basra	747	151	18	578	2.4 %	77%	3,063,059	24.39
Najaf	318	13	6	299	1.9 %	94%	1,549,788	20.52
Muthanna	117	18	4	95	3.4 %	81%	857,652	13.64
Erbil	242	30	1	211	0.4 %	87%	1,953,341	12.39
Kerbala	153	27	8	118	5.2 %	77%	1,283,484	11.92
Sulaymaniya	215	38	4	173	1.9 %	80%	2,277,171	9.44
Missan	52	5	2	45	3.8 %	87%	1,171,802	4.44
Thi-Qar	96	20	4	72	4.2 %	75%	2,206,514	4.35
Kirkuk	72	11	2	59	2.8 %	82%	1,682,809	4.28
Wassit	59	17	3	39	5.1 %	66%	1,452,007	4.06
Diyala	45	19	5	21	11.1 %	47%	1,724,238	2.61
Babylon	49	5	5	39	10.2 %	80%	2,174,783	2.25
Dahuk	26	7	0	19	0.0 %	73%	1,361,211	1.91
Diwaniya	15	3	1	11	6.7 %	73%	1,359,642	1.1
Salah-Addin	13	4	0	9	0.0 %	69%	1,680,015	0.77
Ninewa	12	6	0	6	0.0 %	50%	3,928,215	0.31
Anbar	5	2	0	3	0.0 %	60%	1,865,818	0.27
Total Iraq	4469	1571	160	2738	3.6 %	61%	40,150,174	11.13

cause of death not related to COVID-19 (for example, trauma). There should not be a period of complete recovery between illness and death".¹⁴

Statistical analysis: data was shown by tables and graphs using Microsoft Excel software 2019. To calculate the statistical signifi-

cance of an association, we used t-test used for age, Chi square for travel history and co-morbidities (cardiovascular, hypertension, diabetes mellites, chronic respiratory diseases), and Fischer Exact test for cancer. The association is considered statistically significant if the p value is ≤ 0.05 .





RESULTS

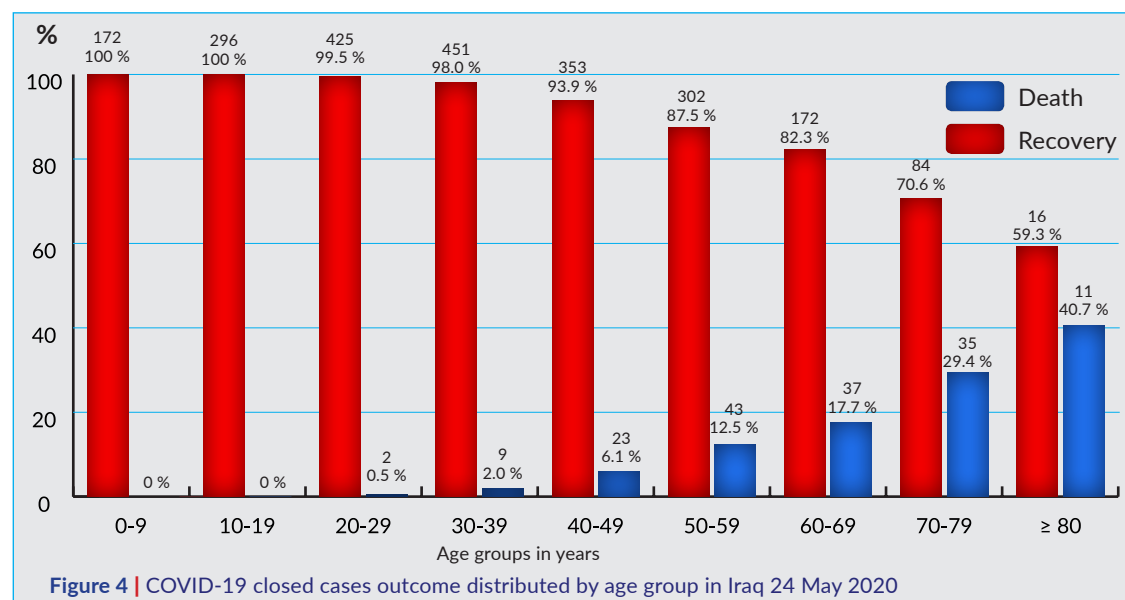
In the first three months of the COVID-19 pandemic, Iraq has registered 4469 confirmed cases of COVID-19. Out of this number, 160 patients have died with a CFR of 3.6 %. **Table 1** shows the distribution of confirmed cases, their outcomes among different Iraqi provinces. Diyala has the highest CFR 5/45 (11.1 %) followed by Babylon 5/49 (10.2%). Dahuk, Salahaddin, Ninewa, and Anbar did not report any death from COVID-19 with a zero CFR.

Figure 1 and 2 show the comparison of Iraqi

CFR and cure rate to that of neighbour countries and the average record of the world up to May 2020. CFR and cure rate are ranking Iraq in the middle among his neighbours.

Age group 50-59 years has included the larger number of death 43/160 (27 %), and the age between 50-80 include about 70 % of the total deaths from COVID-19. **See figure 3**

Figure 4 shows the distribution of the closed cases (recovered or dead) in age groups. In those who were over age of 80 years 40.7 have died and 59.3 have recovered. No death were recorded in people younger than 20 years.



Men died more common than women, 110 (69 %) versus 50 (31 %) **see figure 4. Table 2** shows that mean age in years, gender and having hypertension, coronary artery disease, diabetes mellitus, cancer, and chronic respiratory illness have associated with death all of them with a p value of 0.0001.

DISCUSSION

Death is very dreadful event in any disease. Since the emergence of COVID-19 in December 2019, death was the most fearful fate. The disease is highly contagious but fortunately less fatal.¹⁵ The leading cause of death in patients with COVID-19 is respiratory failure from acute respiratory distress syndrome.¹⁶ renal,

liver, cardiac, coagulopathy, and septic shock might be other causes.¹⁷

Since the first confirmed case of COVID-19 in Iraq in late February 2020, we registered 4469 patients proved to have the disease up to 24 May 2020 with an incidence rate of 11.13 per 100,000 population. (**For more details about the epidemiology of these cases see the article on pages 85-92 of this issue**). Of those diagnosed, 160 patients have unfortunately died with a case fatality rate of 3.6 % ranking Iraq as the ninth among the Eastern Mediterranean Countries, and it is the third among Arabic Asian countries after Yemen and Syria; however, it is much better compared to the world average, 6.3 %.¹⁸ The CFR differs among different provinces in Iraq. The highest is in Diyala and Babylon, 5/45 (11.1 %) and 5/49 (10.2 %) respectively, while the lowest is in Duhok, Salah-Addin, Anbar, and Ninawa , all zero rate, (**see table 1**). The cause for this variability might be due to the number of confirmed cases in these provinces increasing the possibility of death due to an increased number of confirmed cases,

CFR is estimated to be 5.5% based on World Health Organization data as of 18 June 2020. The CFR varies considerably between countries; for example, it is currently higher in countries such as the UK, France, Italy, and Spain, and significantly lower in countries such as Russia, the US, Germany, Australia, Turkey,

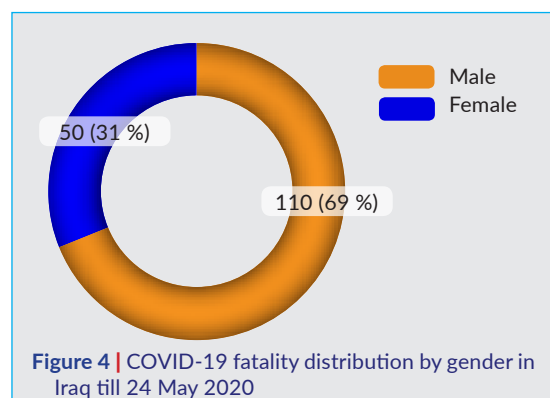


Table 2 | association between some demographic factors and comorbidities with recovery or death

Factor	Death		Recovery		p value
	No.	%	No.	%	
Gender					
Male	110	8%	1202	92%	<0.0001
Female	50	4%	1095	96%	
Age in years					
Mean±SD	59.56±13.22		35.71±18.45		<0.0001
CVD					
Yes	19	53%	17	47%	<0.0001
No	141	6%	2280	94%	
Hypertension					
Yes	43	53%	38	47%	<0.0001
No	117	5%	2259	95%	
Diabetes Mellitus					
Yes	34	50%	34	50%	<0.0001
No	126	5%	2263	95%	
Cancer					
Yes	2	50%	2	50%	
No	158	6%	2295	94%	
Chronic respiratory disease					
Yes	8	53%	7	47%	<0.0001
No	152	6%	2290	94%	
Travel history					
Yes	9	6%	137	94%	0.86
No	151	7%	2160	93%	

Iceland, Singapore, and middle east.¹⁹

We need to be cautious in interpreting these figures as CFRs in pandemics might start high and then declining as more statistics become available. For example, at the start of the 2009 H1N1 influenza pandemic the CFR varied from 0.1% to 5.1% (depending on the country), but the mortality rate ended up being around 0.02%.²⁰

The variability of the CFR among countries and in the same country over different time might be due to the changing definitions of both parameters affecting the calculation of CFR; the number of death and number of infected patients. Asymptomatic or mildly symptomatic patients might not be included in the calculation because many of them are not within the scope of surveillance adopted especially in early days of the pandemic where most of the countries have suffered from the lack of enough number of kits to do wide range surveillance. Also it may be attributed to the

fact that COVID-19 related deaths, at least initially, are not clearly defined in the international reports available so far, and differences in definitions of what is or is not a COVID-19-related death might explain variation in case-fatality rates among different countries.²¹ One can not ignore the effect of politics and immaturity of some health systems on this variability.

Age was seen in our study to be directly related to case fatality rate and indirectly related to cure rate. The more the age was, the more the case fatality and the less the recovery rate were. About 126 (79 %) of deaths were 50 years and above. As seen in **figure 3** the mean age of those died from COVID-19 was 59.56±13.22 while the mean for recovered patients was 35.71±18.45, p value <0.0001.

Studies from many countries have agreed with our results regarding the age. The majority of deaths in China have been in patients aged 60 years and older.²² In Italy, the CFR was 8.5% in patients aged 60 to 69 years, 35.5% in patients aged 70 to 79 years, and 52.5% in patients aged ≥80 years.²³ In the US, the CFR was highest among patients aged ≥ 85 years (10% to 27%), followed by those aged 65 to 84 years (3% to 11%).²⁴

The susceptibility of elderly patients to have severe infection, development of ARDS and high mortality can be attributed to their low immunity and high rate of comorbidities.^{25, 26}

In Iraq during the first three months of pandemic of COVID-19, Males were mildly predominant than female in the number of confirmed cases, 2430 (54 %) versus 2039 (46)¹⁸; however, the mortality is remarkably higher in males, 110 (69%) versus 50 (31 %), p value <0.0001. Most of the preliminary reports have shown similar results. In Italy, the male to female ratio was 3:1.²⁷ Similarly, the weekly surveillance reports of all European countries issued by the WHO office for Europe has shown that death from COVID-19 in men were 68 %, 61 %, and 58% in epi week 14, 17, and 22 respectively.²⁸ However, a study from Wuhan in China has shown that 52 % of deaths were women but this was statistically non-significant.²⁹

Although the final data about the effect of gender on the COVID-19 and its mortality have not reached yet, many explanations were made. The explanations can be grouped

into three, the **first** is the genetic differences between male and female. The **second** is the behavioural differences between them and the **third** is the difference in the chances of exposure. The second and the third might not have a strong base to be defeated but the first has scientific bases. Several studies have proposed plausible mechanisms for the protective effect of female sex hormone in sepsis.³⁰ Males and females respond differently to many RNA and DNA virus infections, in general, males generate less robust immune responses and are more susceptible to a variety of infectious agents. In contrast, females mount stronger innate and adaptive immune responses and are relatively resistant to virus infections.³¹

We studied any association between mortality and having hypertension, coronary artery disease, diabetes mellitus, cancer and chronic respiratory disease. All have shown a statistically significant association with mortality, p value of < 0.0001. Specific comorbidities have been reported to be associated with increased risk of infection, its severity, and worse outcomes including mortality. The most common comorbidities in one report were hypertension (30%), diabetes (19%), and coronary heart disease (8%).³² Similarly in Italy, the commonest three comorbidities associated with death from COVID-19 were hypertension (69%), diabetes (32%), ischemic heart disease (27%).³³ Another study revealed that hypertensive COVID-19 patients tend to show higher mortality. Previous clinical studies on SARS and Middle East respiratory syndrome showed that hypertension is a risk factor for increased mortality in infected patients, the imbalance of cytokines may be considered an explanation for the correlation between hypertension and severe COVID-19.³⁴ DM was associated with mortality, severe COVID-19, ARDS, and disease progression in patients with COVID-19, Yan et al have shown that patients with diabetes and severe covid-19 have higher proinflammatory cytokines and a worse survival rate than non-diabetics.^{35, 36}

CONCLUSION

CFR of COVID in Iraq is in the middle rank as compared to the neighbour countries and about half of the average of the world. Diyala and Babylon

have reported the highest CFR in Iraq, while Dohuk, Salahaddin, Ninawa, and Anbar have reported no deaths so far. Being a male, elderly, and having a chronic medical illness is statistically associated with death.

REFERENCES

1. Sun J, He WT, Wang L, Lai A, Ji X, Zha X, et al. COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives'. *Trends in Molecular Medicine*, May 2020;26(5):483-495. <https://doi.org/10.1016/j.molmed.2020.02.008>
2. Chan KW, Wong VT, and Tang S. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese–Western Medicine for the Management of 2019 Novel Coronavirus Disease. *The American Journal of Chinese Medicine*, 2020;48(3):737–762. DOI: 10.1142/S0192415X20500378
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; March 28; 395: 1054–62.
4. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol* 2020;92:568–576. DOI: 10.1002/jmv.25748
5. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020 Apr 30;382(18):1708-1720. doi: 10.1056/NEJMoa2002032.
6. WHO. Coronavirus disease 2019 (COVID-19) Situation Report – 73. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200402-sitrep-73-covid-19.pdf?sfvrsn=5ae25bc7_6. Accessed on 10 June 2020.
7. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Yiming Li. The epidemiology, diagnosis and treatment of COVID-19. *Int J Antimicrob Agents*. 2020 May; 55(5): 105955.
8. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical Characteristics of COVID-19 Patients with Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multi-center Study. *Am J Gastroenterol* 2020;115:766–773.
9. Riou J, Hauser A, Counotte MJ, Althaus CL. Adjusted Age-Specific Case Fatality Ratio During The Covid-19 Epidemic In Hubei, China, January And February; medRxiv; 2020; March 6. doi: <https://doi.org/10.1101/2020.03.04.20031104>
10. Worldometer website; access on <https://www.worldometers.info/coronavirus/#countries>
11. Banerjee A, Pasea L, Harris S, Gonzalez-Izquierdo A, Torralbo A, Shallcross L, et al. Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study. *Lancet* 2020;395(10238):1715-1725.
12. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ* 2020; 368 :m1198.
13. Biswas R. Are Men More Vulnerable to Covid-19 as compared to Women? *Biomed J Sci & Tech Res* 2020;27(2):20645-20646. DOI: 10.26717/BJSTR.2020.27.004481
14. WHO. International Guidelines For Certification and Classification (Coding) of COVID-19 as Cause Of Death. 16 April 2020. Available from: https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19.pdf

15. Goh GK, Dunker AK, Foster JA, Uversky VN. Shell disorder analysis predicts greater resilience of the SARS-CoV-2 (COVID-19) outside the body and in body fluids. *Microb Pathog*. 2020;144:104177. doi:10.1016/j.micpath.2020.104177
16. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020 May;46(5):846-8.
17. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R and Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. *Biology of Sex Differences*, 2020;11:29. <https://doi.org/10.1186/s13293-020-00304-9>.
18. Alhilfi RA, Majeed YY, Bannoosh AK, Ali SS, Shnan BA, Muf-tin AB. Epidemiological Characteristics of confirmed COVID-19 cases in Iraq, three months situation analysis. *Iraqi New Medical Journal* 2020 July; 6(12):85-92.
19. World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020. Available from: https://www.who.int/docs/default-source/coronavirus/situation-reports/20200618-covid-19-sitrep-150.pdf?sfvrsn=aa9fe9cf_4
20. Oke J, Heneghan C. Global Covid-19 Case Fatality Rates. From Centre for Evidence-Based Medicine 2020 [internet publication]. available from: <https://www.cebm.net/covid-19/global-covid-19-case-fatality-rates/>. Last updated on 9 June 2020, accessed on 20 June 2020.
21. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA* May 12, 2020;323(18):1775-1776.
22. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China [in Chinese]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020 Feb 17;41(2):145-51.
23. Sorbello M, El-Boghdady K, Di Giacinto I, et al. The Italian COVID-19 outbreak: experiences and recommendations from clinical practice. *Anaesthesia*. 2020 Jun;75(6):724-32.
24. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19): United States, February 12 - March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020 Mar 27;69(12):343-6.
25. Moraga P, Ketcheson DI, Ombao HC, Duarte CM. Assessing the age- and gender-dependence of the severity and case fatality rates of COVID-19 disease in Spain. *Wellcome Open Research* 2020;5:117. Available from: <https://doi.org/10.12688/wellcomeopenres.15996.1>.
26. Wu C, Chen X, Cai Y, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. Published online March 13, 2020. doi:10.1001/jamainternmed.2020.0994.
27. Di Stadio A, Ricci G, Greco A, de Vincentiis M, Ralli M. Mortality rate and gender differences in COVID-19 patients dying in Italy: A comparison with other countries. *Eur Rev Med Pharmacol Sci*. 2020;24(8):4066-4067. doi:10.26355/eur-rev_202004_20980].
28. WHO. Regional office for Europe. COVID-19 weekly surveillance report. Available from: <https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/previous-weekly-surveillance-reports>
29. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J*. 2020;55(5):2000524. Published 2020 May 7. doi:10.1183/13993003.00524-2020
30. Mohamad Alkhoul, MD, Aravinda Nanjundappa, MD, Frank Annie, PhD, Mark C.Bates, MD, DSc, Deepak L. Bhatt, MD, MPH; Sex Differences in COVID-19 Case Fatality Rate: Insights From a Multinational Registry. *Mayo Clin Proc*. 2020;95; <https://doi.org/10.1016/j.mayocp.2020.05.014>
31. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, and Perlman S; Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection; *J Immunol* 2017; 198:4046-4053; doi: 10.4049/jimmunol.1601896.
32. Schiffrin EL, Flack JM, Ito S, Muntner P, and Webb RC. Hypertension and COVID-19. *American Journal of Hypertension* 2020;33(5):373-374.
33. Statista. Most common comorbidities in COVID-19 deceased patients in Italy 2020. Available from: <https://www.statista.com/statistics/1110949/common-comorbidities-in-covid-19-deceased-patients-in-italy/>. Accessed on 10 June 2020.
34. Huang S, Wang J, Liu F, Liu J, Cao G, Yang C. COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study. *The Japanese Society of Hypertension* May 2020. Available from: <https://doi.org/10.1038/s41440-020-0485-2>.
35. Huang I, Lim MA, Pranata R. Diabetes & Metabolic Syndrome: Clinical Research & Reviews; Diabetes & Metabolic Syndrome. *Clinical Research & Reviews* 14 (2020). Diabetes Metab Syndr. 2020 July-August; 14(4): 395–403. Published online 2020 Apr 17. doi: 10.1016/j.dsx.2020.04.018.
36. Shenoy A, Ismail M, Bajaj M. Diabetes and covid-19: a global health challenge. *BMJ Open Diab Res Care* 2020;8:e001450. doi:10.1136/bmjdr-2020-001450.



Abbreviations list: Acute respiratory distress syndrome (ARDS), Case fatality rate (CFR), Coronary artery disease (CAD), Coronavirus disease 2019 (COVID-19), Deoxyribonucleic acid (DNA), Middle east respiratory syndrome corona virus (MERS-CoV), Polymerase chain reaction (PCR), Ribonucleic Acid (RNA), Severe acute respiratory syndrome corona virus (SARS-CoV), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), United Kingdom (UK).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this study a part from self funding.

Anaemia profile in children with ESRD on haemodialysis: a descriptive study from the Central Teaching Hospital of paediatrics in Baghdad

Layla Qasim H. Ali¹

ABSTRACT

INTRODUCTION: Anaemia is a recognized complication of chronic kidney disease. Reduction of erythropoietin production is a major cause; however, many other factors may play a role. Accurate search for the cause with proper treatment is essential to have a good response.

OBJECTIVE: To determine the mean haemoglobin level and type of Iron deficiency anaemia in anaemic paediatric patients with ESRD who are on regular haemodialysis and erythropoietin And to find any correlation between the mean Hb level and some demographic, haematologic and biochemical factors.

METHODS: Analytical cross-sectional study conducted at Central Teaching Hospital of Paediatrics in Baghdad/Iraq from the 1st of October 2018 to the 30th of May 2019. Patients involved were those diagnosed as end stage renal disease with anaemia, and on regular haemodialysis and used of erythropoietin injections. Mean Hb level and other haematologic and biochemical indices were measured and tested for any correlation between them.

RESULTS: The mean age was 9.54 ± 3.67 years and the mean of Hb was 7.99 ± 1.48 g/dl. The mean Hb level for males was 7.87 ± 1.63 g/dl, and for female was 8.13 ± 1.30 g/dl. The mean serum iron level was 24.12 ± 19.57 micromol/L, the mean serum ferritin was 617.87 ± 439.83 ng/ml. The commonest type of anaemia found within the sample was the normochromic normocytic in 23 (46%) and the least was the macrocytic in 2 (4%). Hyperferritinaemia present in 30 patients (60%), while functional iron deficiency anaemia in 14 patients (7%) and absolute iron deficiency anaemia in 10 patients (5%).

CONCLUSION: The mean Hb level in our paediatric patients with ESRD who were on haemodialysis was still low despite using erythropoietin injections. The majority of anaemia is an absolute iron deficiency. Dose of the erythropoietin used, s. creatinine, parathyroid hormone, cause of renal failure, type of vascular access, s. ferritin level, and transferrin saturation were found to have a significant correlation with the mean Hb level.

Key words: Anaemia, Haemodialysis, Iron deficiency, Haemoglobin, ESRD.

INTRODUCTION

Anaemia is a frequent complication of chronic kidney diseases (CKD) in children and adults.¹ The major cause of anaemia in patients with chronic kidney disease and end-stage renal disease (ESRD) is the reduction of erythropoietin (EPO) production from the Kidneys.² However, among patients on haemodialysis (HD), several other factors may also contribute to anaemia such as increased destruction of red blood cells due to chemical effects of uremic toxins, blood loss (usually occult) due to platelet dysfunction, blood loss due to clotting inside haemodialyzers and sets during HD sessions, haemolysis associ-

ated with contamination of dialysate water, and water-soluble losses of folate and vitamin B12 through hemodialyzer membranes affecting red blood cell production.³

Anaemia, partially or wholly, may be responsible for many symptoms that have been historically attributed to uraemia. Its manifestations occur due to the effects of decreasing oxygen delivery to tissues and to the consequent compensatory changes of the heart.⁴ Cardiovascular problems are the main causes of death among patient on HD, and anaemia imposes an overload on cardiac function, ultimately provoking left ventricular hypertrophy (LVH): a well-recognized marker of morbidity

¹ MBCHB, FICMS (Paediatrics), FICMS (Nephrology). Senior Paediatric Nephrologist at the Child Central Teaching Hospital, Baghdad, Iraq. E mail: Layla.aloka@gmail.com, Layla_qasim@yahoo.com.

and mortality.⁵ Effect of anaemia and its early treatment on development or regression of LVH is well documented.^{6,7}

The cutoff point for diagnosing anaemia in child patient with CKD is vary among the guidelines. K/DOQI anaemia guidelines states that anaemia is present in the paediatric patient with CKD when the observed haemoglobin is less than the fifth percentile of the normal, adjusted for age and sex.⁵ While KDIGO Clinical Practice Guideline for anaemia in CKD and the European Best Practice Guidelines (EPBG) report that anaemia is diagnosed if HB is < 12 g/dl in prepubertal age and < 11 g/dl in post puberty about age of 12 years.^{8,9} The National Health and Nutrition Examination Survey (NHANES) III Study showed that the fifth percentile for haemoglobin (Hb) may vary by as much as 2.8 gm/dl from younger to older boys and by 2 gm/dl for girls and boys of a similar age group.¹⁰

The choice of Hb targets for treating patients with renal anaemia is still a matter of great debate.^{11,12} The current practice aims at only partial correction of anaemia. The concern is that complete correction of anaemia in CRF patients may increase risk of adverse events such as arterial hypertension and vascular access thrombosis.¹² For patients with cardiovascular disease, an Hb concentration limited to 11-12 g/dl is suggested.^{13,14}

The majority of patients who have CKD and anaemia respond to erythropoietin therapy, although a minority show a more sluggish response, which may be due to iron insufficiency, inflammation, or a number of other minor factors.^{15,16}

Children with CRF are especially prone to iron deficiency due to increased iron requirements for growth and rHuEPO-facilitated erythropoiesis, which is associated with decreased iron intake and absorption, chronic blood loss, and iron sequestration secondary to chronic inflammatory processes.¹⁷ Approximately 43-90% of paediatric patients undergoing HD experience iron deficiency.¹⁸ Uraemia is a chronic inflammatory state, and increased hepcidin production under this condition may explain iron deficiency in the majority of patients with ESRD.¹⁹

Iron deficiency may be absolute that needs iron replacement for adequate Epo response²⁰

or functional when there is a failure to release iron rapidly enough to keep pace with the demands of bone marrow for erythropoiesis, despite adequate or even increased body iron stores. It is confirmed and resolved by administering iron intravenously in a readily available form.²¹

Iron status is evaluated by both the serum ferritin and transferrin saturation levels. While serum ferritin levels reflect total iron body stores, it is also an acute phase reactant and may be elevated in the face of systemic inflammation or malnutrition, compromising its ability to serve as a reliable measure of iron status when its value is elevated. The target serum ferritin level in the absence of inflammation is >100 ng/ml and a low serum ferritin level has been shown to be a specific predictor of iron deficiency in paediatric CKD.²² Transferrin saturation (TSAT) is a measure of iron immediately available for haemoglobin synthesis. It is typically expressed as a percentage and is calculated as the serum iron divided by total iron binding capacity multiplied by 100%, with a therapeutic target of greater than 20% in patients with CKD.²³

Other tests of iron status, such as percentage of hypochromic red blood cells and reticulocyte Hb content may be used instead of, or in addition to, TSAT and ferritin levels if available. Measurement of hepcidin levels has not been shown to be clinically useful or superior to more standard iron status tests in patients with CKD.²⁴ Iron can be supplemented orally or intravenously. Intravenously (IV) administered iron is well tolerated by the majority of patients. However, experience with IV iron therapy in children with CRF is based on a few small paediatric trials.²⁵

Although the role of anaemia and its treatment in CKD is widely studied in adults, studies in children are relatively scarce. And in Iraq it is rather very rare. So, this study was designed to describe the mean HB level and types of Iron deficiency anaemia reported in children with CKD who are on regular haemodialysis and using erythropoietin therapy at the Al-Zohoor Haemodialysis centre in the Central Teaching Hospital of Paediatric in Baghdad. And to find the association between mean Hb level and some demographic, Haematologic and biochemical factors.

METHODS

Settings and study design: An analytic cross-sectional study conducted at Al- Zohoor Haemodialysis Centre at the Central Teaching Hospital of Paediatrics in Baghdad from the 1st October 2018 to 30th of May 2019. The Central Teaching Hospital of paediatric is the major paediatric hospital in Al-Karkh District in Baghdad, Iraq. It provides haemodialysis services to children from Baghdad and nearby provinces.

Ethical consideration: The research protocol was approved by institutional ethical committee and agreement was taken from the administration of the Central Teaching Hospital of paediatrics. The study has been conducted in accordance to the terms of the code of ethics in research of Ministry of Health in Iraq.

Definition of the cases, inclusion and exclusion criteria: Paediatric patients of both genders who were diagnosed by senior nephrologists in our centre as having ESRD and on chronic regular haemodialysis and having anaemia were included in this study. Paediatric age was defined in our inclusion criteria as age less than eighteen years. Chronic regular dialysis was defined as three-hour session three times a week for at least three months. All children on HD were receiving regular doses of erythropoietin (rHuEPO) to stimulate erythropoiesis, according to KDOQI guidelines for the treatment of anaemia in haemodialysis subjects.²³ Patient who had incomplete investigations, irregular sessions of dialysis, acute kidney injury needed short term dialysis, or normal Hb level according to K/DOQI guidelines were excluded from the study.

Sampling: We enrolled all registered patients who fulfil the inclusion criteria in were visiting our centre to undergo scheduled haemodialysis sessions during the studies period.

Data collection and procedure: Patients' data were taken from their monthly records. The data have included age, gender, cause of ESRD, Hb level, creatinine level, dose of rHuEPO (unit/kg/week). Serum iron, serum ferritin, total iron binding capacity (TIBC), transferrin saturation (TSAT) were done for all patients at least once during the study period due to shortage of resources. Transferrin saturation percentage was calculated by the formula $TSAT (\%) = \text{Iron}/TIBC \times 100$.²³ All routine

laboratories measurements were performed by using automated methods in the central laboratories of our hospital. Serum intact parathyroid hormone (PTH) was measured by a chemiluminescence immunoassay which were done in a private reference laboratory because they were not available in our hospital at the time of the study.

In accordance with the National Kidney Foundation of America NKF-K/DOQI Guideline, anaemia was diagnosed in our study as a haemoglobin level less than 11g/Ld. Ferritin greater than 200 ng/ml was considered as hyperferritinemia. Functional iron deficiency anaemia (IDA) was diagnosed when TSAT % was less than 20% and serum ferritin level was more than 100 ng/ml.²³ While absolute iron deficiency anaemia was diagnosed as TSAT % of less than 20% and serum ferritin of less than 200 ng/ml.²³

In our hospital, the reference value of the mean corpuscular volume (MCV) is 80-94 fl, and the mean corpuscular haemoglobin concentration (MCHC) is 32-36 %. Blood films were recommended routinely for all patients for definition of the types of anaemia as normochromic normocytic, hypochromic microcytic, dimorphic and macrocytic anaemia. All blood films were read by an experienced haematologist at our institution. Inflammatory markers like CRP was not included in our study despite its importance on analysis the response to erythropoietin because it was not universally available at the time of the study. Also, we could not include the type, dose and way of administration of Iron in our study because the data were inconsistently available for variety of reasons.

Mean HB levels were correlated with gender, cause of ESRD, type of vascular access whether intravenous (IV) line or Arteriovenous fistula (AVF), and types of anaemia; normocytic, microcytic dysmorphic or macrocytic.

Statistical analysis: The data were analysed by version 21 SPSS software. Analysis of variance (ANOVA) used to find the significance of mean difference of the continuous variables of more than two categories, with a p value of less than or equal to 0.05 regarded as significant. Bivariate correlation between 2 continuous variables, with a p value of less than or equal to 0.05 is regarded as significant. Pearson test

Table 1 Means of some variables of the sample with their correlation to the mean of haemoglobin.

Variable	Mean	± SD	Statistics
Hb (g/dl)	7.99	1.48	
Age (years)	9.54	3.67	Pearson r = + 0.121 P = 0.403 (NS)
EPO dose U / Kg / Week	114.44	39.34	P = 0.043*
S. Creatinine (mmol)	565.09	214.88	Pearson r = - 0.358 P = 0.011*
PTH (pg / ml)	548.24	411.29	Pearson r = - 0.364 P = 0.009**
MCV (fl)	72.53	17.19	P = 0.079 (NS)
MCHC (g/L)	38.77	15.09	P = 0.160 (NS)
S. Iron (micromole/L)	24.12	19.57	P = 0.927 (NS)
S. Ferritin (ng/ml)	617.87	439.83	P = 0.004**
TSAT%	34.67	18.79	P = 0.023*
TIBC	41.99	20.58	P = 0.121 (NS)

* Statistically significant at alpha level of less than 0.05 (NS) Not significant

** Statistically significant at alpha level of less than 0.01

was used to measure correlation coefficient (r) in order to find any correlation between Hb level of other factors.

RESULTS

The study analyses the records of 50 children who were on regular haemodialysis at the Central Teaching Hospital of Paediatrics in Baghdad/Iraq. **Table 1** shows the mean levels of some numerical variables with their correlation to the mean Hb level. The mean of haemoglobin ± standard deviation (SD) was 7.99 ± 1.48 g/dl. The mean age ± SD of patients in the study was 9.54 ± 3.67 years. The mean (SD) rhEPO dose was 114.44 ± 39.34 IU/kg/wk. The mean (SD) serum creatinine was 565.09

± 214.88 mmol and the mean PTH level was 548.24 ± 411.29 pg/ml. For other variables see **table 1**.

Table 1 also shows that the dose of EPO and s. ferritin have a significant positive correlation, while s. creatinine, level of parathyroid hormone, TSAT % have a negative statistically significant correlation.

Table 2 shows the distribution of our sample among some categorical variables like gender, cause of ESRD, vascular access, and types of anaemia. Then the correlation of these variables with the mean Hb level. Males were 27 patients (54%) with a mean Hb of 7.87 ± 1.63 g/dl and 23 patients (46 %) were females with their mean Hb level of 8.13 ± 1.30 g/dl. This difference of the mean Hb level with gender was statistically non-significant. Tubular causes, CV line as a vascular access, and normochromic normocytic anaemia were the commonest among our sample 21 patients (42 %), 39 (78%), and 23 (46%) respectively. Tubular causes has the least Hb level 7.14 ± 1.26 , while the highest mean Hb level was associated with anatomical causes and this was statistically significant correlation (p value 0.001). IV access was associated with lower mean Hb level compared to AVF but this correlation was insignificant for IV line but significant for AVF (p value 0.028).

Hyperferritinaemia found in 30 patients (60%), functional iron deficiency anaemia in 14 patients (7 %), and absolute iron deficiency anaemia in 10 patients (5%). **See table 3**

Table 2 Frequency distribution of the sample and correlation with Hb (total number is 50)

Variable		No (%)	Mean Hb in g/dl	± SD g/dl	Statistics
Gender	Male	27(54)	7.87	1.63	P=0.057(NS)
	Female	23 (46)	8.13	1.30	
Aetiology of renal failure	Anatomical	18 (36)	8.83	1.37	P= 0.001**
	Glomerular	11 (22)	8.24	1.21	
	Tubular	21 (42)	7.14	1.26	
Vascular access	AVF	11 (22)	8.21	1.44	P= 0.028*
	CV line	39 (78)	7.22	1.39	P= 0.051 (NS)
Type of anaemia	Normochromic normocytic	23(46)	8.26	1.58	
	Hypochromic Microcytic	19 (39)	7.80	1.41	
	Dimorphic	6 (12)	7.68	1.56	
	Macrocytic	2 (4)	7.65	0.91	

* Statistically significant at alpha level of less than 0.05 (NS) Not significant

** Statistically significant at alpha level of less than 0.01

Table 3 | Frequency distribution according to type of IDA. (Total number is 50 Patients)

Variable		Frequency	%
Hyperferritinemia	Yes	30	60
	No	20	40
Functional IDA	Yes	7	14
	No	43	86
Absolute IDA	Yes	5	10
	No	45	90

DISCUSSION

Our study was conducted on a small sample of patients in which data were collected retrospectively making it rather difficult to include and analyse all necessary parameters for this topic. Studies on anaemia in children with ESRD on haemodialysis are scarce and most of our comparisons were made with data of the adults. These limitations should draw our attention towards conducting many high quality and large sample studies on paediatric age group in the future.

The mean Hb level in our sample was 7.99 g/dl. A higher level of Hb was found in a study from Iran where the mean Hb was 9.6 ± 1.9 g/dl.²⁶ Frankenfield et al have found that over one third of children ages 12 -18 maintained on chronic haemodialysis have a mean haemoglobin level of less than 11 g/dl.⁹ Our lower level of HB may be due to the fact that our sample has included only patients with abnormal HB level. Poor adherence or unavailability of essential medications, in addition to racial and socioeconomic differences could explain this result.

The mean age of patients in our study was 9.54 ± 3.67 years, and it has no significant association with the mean Hb level. A result which is comparable to a study in Brazil.²⁷ The mean rhEPO dose was 114.44 ± 39.34 IU/kg/wk and it has a statistically significant association with the mean Hb level ($p=0.043$). This agrees with Azhir et al's results.²⁸

Also, a statistically significant negative correlation was seen between mean Hb level and serum creatinine (P value 0.011). The more the serum creatinine level was, the less Hb. Madonre has similarly found that serum creatinine is inversely correlated with Hb levels.²⁹

Few studies on the correlation between PTH and Hb have been conducted in children with CKD on regular dialysis, and those that exist have been limited by small sample size as in our study where we found that the mean PTH level was $548.24(\pm 411.29)$ pg/ml and it has a statistically significant inverse correlation with the mean level of Hb. Seeherunvong found that the children who required higher doses of erythropoietin stimulating agents (ESAs) due to less Hb level had higher serum iPTH levels.³⁰ This high level of PTH in our study indicates high turnover bone disease secondary to hyperparathyroidism which in turn impairs erythropoiesis either by higher degree of bone marrow fibrosis or deficiency of calcitriol with increase in red blood cells haemolysis.³¹ This is an important issue that must be evaluated addressed in our daily practice because it is a major cause of erythropoietin hyporesponsiveness.²⁸

Most of the patients were males 27 (54%), and higher Hb level was found in females (8.13 g/dl) compared to that in males (7.87g/dl). There was no significant correlation of the mean Hb level and gender of the study population. A corresponding study in Korea found that the rate in males is 54.2% which is slightly higher than that in females 45.8 %; However, the association between Hb and gender was not significant.³² Frankenfield et al⁹ found that female had higher prevalence of anemia than males. While Mitra Mahdavi-Mazdeh et al found that there was negligible difference of Hb level according to gender and no significant correlation between them.³³

The most common aetiology of ESRD in the study was the tubular 21 (42 %) followed by anatomical causes 18 (36 %). Patients with tubular causes has less Hb level an association which was statistically significant. (P value 0.001)

This is may be due to the fact that tubular diseases with tubularglomerular feedback injury is a major contributor to loss of renal function.³⁴ Tubular diseases may be overlooked and not fully understood and managed with the lack of genetic diagnosis in our country. Besides, most of tubular diseases are inherited in nature and expected to be more common in countries like ours where positive consan-

guinity marriages occur frequently. Contrary to ours, Frankenfield has found that anatomical causes were the prevalent cause of ESRD and that the causes have not shown a statistically significant correlation with Hb level.⁹

In our study, 39 patients (78 %) were using the central venous (CV) line, and the other 11 (22 %) were using arteriovenous fistula (AVF). This may be due to technical and surgical challenges in creating AVF especially in children with low body weight, and the families' desire to avoid surgical intervention. The mean Hb level in those dialysed through a catheter access was 7.22 ± 1.39 g/ dl, a level which is slightly lower than the mean in those using AVF which was 8.21 ± 1.44 g/ dl. However, this difference has not shown a statistically significant correlation. Similarly, Frankenfield⁹ has found that the HB level is lower in patients using vascular access than using AVF, 9.8 versus 10.6. This can be explained by the association of the anaemic state with inflammatory states with the use of vascular access and the presence of co-morbidities in many HD patients. Patients with inflammatory states would have EPO resistance and, thus, lower Hb levels.²⁸

The analysis of red blood cell indices shows that there was no statistically significant correlation for Hb level with the MCV and MCHC. The commonest type of anaemia found within the sample was the normochromic normocytic anemia, and there was no statistically significant correlation between type of anemia and level of Hb. Azhir et al found that MCV levels remained stable during follow-up, and MCHC increase more than (20%) of normal,²⁸ while Hayder et al, in a study at Hawler Teaching Hospital, has found that MCV stay unchanged while MCHC decrease with the predominance of microcytic anaemia.³⁵ The unchanged MCV in some patients is explained by the concomitant occurrence of both iron deficiency anaemia and EPO deficiency. The correlation between Hb level and RBC indices and type of anaemia failed to be significant and the cause was unclear.²⁸ The measurements of MCV and MCHC are hopelessly insensitive in diagnosing iron deficiency in that by the time their values fall below normal, iron deficiency is well advanced.²¹

Regarding the correlation of Iron indices to

the mean Hb level, mean serum Iron and TIBC levels did not show a statistically significant correlation, while mean serum ferritin showed a positive correlation and TSAT % showed a negative correlation both with a statistical significance.

Madore et al²⁹ in their study also have found a significant correlation between Hb level, and S. Ferritin and TSAT %, but he, in contrary to what we found, has shown that S. Iron is significantly correlated to the Hb level stresses on the importance of Iron to optimise the response to erythropoietin.²⁹ Our different result regarding S. Iron may be due to the small sample that we have in our study or the difference in the target because his target was adults.

Hyperferritinemia was found in 30 patients of our sample (60%). Biniiaz from Iran has found it 80.4 % of his sample.³⁶ High S. Ferritin despite low levels of Iron indices may be due to impaired iron metabolism or being a response to nonspecific systemic inflammatory process rather than a real increase in iron store.²⁹ Due to lack of data, we could not identify the presence of chronic co-morbid inflammatory diseases that their presence could adversely influence the response to erythropoietin. Thus, the serum ferritin in this context may not only be unhelpful, but may even be misleading.

On the other hand, we found functional iron deficiency anaemia in 7 patients (14 %) and absolute iron deficiency anaemia in 5 patients only (10%). Relative iron deficiency anaemia in this study could be a manifestation of poor nutrition, poor and irregular iron supplementation, patient's intolerance to iron and lack of full investigations to cover causes of iron deficiency. A study in Spain on haemodialysis patients finds that 39 % of them had an absolute iron deficiency and 21 % had a functional iron deficiency.²⁶ A study in Iran has reported the prevalence of absolute and functional iron deficiency anaemia were 11 and 24 % respectively.³⁷

CONCLUSION

The mean Hb level in our paediatric patients with ESRD who were on haemodialysis

was still low despite using erythropoietin injections. The majority of anaemia is an absolute iron deficiency. Dose of the erythropoietin used, s. creatinine level, level of PTH, cause of renal failure, type of vascular access, s. ferritin level, and TSAT % were found to have a significant correlation with the mean Hb level. .

REFERENCES

- Kher k ,Schnaper H,Makker S (Ed).(2007,p341).Clinical pediatrics nephrology:Chronic kidney disease. 2nd ed.informa healthcare.
- Chavers BM, Roberts TL, Herzog CA, et al. Prevalence of anemia in erythropoietin-treated pediatric as compared to adult chronic dialysis patients. *Kidney Int.* 2004; 65(1): 266-73
- Bowry SK, and Gatti E. Impact of hemodialysis therapy on anemia of chronic kidney disease: the potential mechanisms. *Blood Purification*, 2011;32(3):210-219.
- Peco-Antic A. Management of renal anaemia. *Turk J Pediatr* 2005;47 (supplement): 19-27.
- Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, & Barre PE. The impact of anemia on cardiomyopathy, morbidity, and mortality in endstage renal disease. *American Journal of Kidney Diseases* 1996;28(1):53-61.
- Pascual J, Teruel JL, Moya JL, Liaño F, Jimenez Mena M, Ortuño J. Regression of left ventricular hypertrophy after partial correction of anemia with erythropoietin in patients on hemodialysis: a prospective study. *Clin Nephrol* 1991;35: 280-287.
- Parfrey PS, Foley RN, Wittreich BH, et al. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *J Am Soc Nephrol.* 2005;16:2180-2189.
- KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney International*. Supplements (2012) 2, 292–298; doi:10.1038/kisup.2012.34.
- Frankenfield DL, Neu AM, Warady BA, et al. Anemia in pediatric hemodialysis patients: results from the 2001 ESRD clinical Performance Measures Project. *Kidney Int.* 2003;64(3): 1120-1124.
- VanDeVoorde R., Warady B A (2006.), Pediatric Nephrology, Management of Chronic Kidney Disease.6th ed. Springer-Verlag Berlin Heidelberg 2009.
- Clinical practice recommendations for anemia in chronic kidney disease in children. *Am J Kidney Dis* 2006;47:S86–108.
- Muirhead N. A rationale for an individualized haemoglobin target. *Nephrol Dial Transplant* 2002;17(Suppl): 2-7.
- Besarab A, Bolton WK, Browne JK, et al. The effect of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;339:584-590.
- European best practice guidelines for the management of anemia in patients with chronic renal failure. *Nephrol Dial Transplant* 1999;14(Suppl):S1-S176.
- Ohashi N, Sakao Y, Yasuda H, & Kato A, Fujigaki Y. Methoxy polyethylene glycol-epoetin beta for anemia with chronic kidney disease. *International Journal of Nephrology and Renovascular Disease* 2012;5:53-60.
- Johnson DW, Pollock CA, and Macdougall IC (2007). Erythropoiesis-stimulating agent hyporesponsiveness. *Nephrology* 2007;12(4): 321–330.
- Leonard MB, Donaldson LA, Ho M, Geary DF. A prospective cohort study of incident maintenance dialysis in children: an NAPRTC study. *Kidney Int* 2003;63:744-755.
- Warady BA, Kausz A, Lerner G, et al. Iron therapy in the pediatric hemodialysis population. *Pediatr Nephrol* 2004;19(6): 655-661.
- Agarwal R, Warnock D. Issues related to iron replacement in chronic kidney disease. *Seminars in Nephrology* 2002;22:479-487.
- Koshy SM, Geary DF. Anemia in children with chronic kidney disease. *Pediatr Nephrol* 2008;23: 209–19.
- Macdougall IC. , Kai-Uwe Eckardt (2010 .79-954). Anemia in Chronic Kidney Disease, COMPREHENSIVE CLINICAL NEPHROLOGY 4th ed. Saunders, an imprint of Elsevier Inc.
- VanDeVoorde R., Warady B A (2006.), Pediatric Nephrology, Management of Chronic Kidney Disease.6th ed. Springer-Verlag Berlin Heidelberg 2009.
- Levin A, Rocco M. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. *Am J Kidney Dis.* 2006;47(5 Suppl 3):S11-S145. DOI: 10.1053/j.ajkd.2006.03.010
- Tessitore N, Girelli D, Campostrini N et al. Hepcidin is not useful as a biomarker for iron needs in haemodialysis patients on maintenance erythropoiesis-stimulating agents. *Nephrol Dial Transplant* 2010;25:3996-4002.
- Van Damme-Lombearts R, Broyer M, Businger J,Baldauf C, Stocker H. A study of recombinant human erythropoietin in the treatment of anemia of chronic renal failure in children on hemodialysis. *Pediatr Nephrol* 1994; 8: 338-342.
- Vahid Pourfarziani, Fahimeh Ghanbarpour, Eghlim Nemati, Saeed Taheri, Behzad Einollahi. Renal Data from Asia-AfricaLaboratory Variables and Treatment Adequacy in Hemodialysis Patients in Iran. *Saudi J Kidney Dis Transpl* 2008; 19(5):842-846.
- De Freitas JS, Costa PS, Costa LR, Naghettini AV. Evaluation of clinical and laboratory variables associated with anemia in pediatric patients on hemodialysis. *Jornal de Pediatria* 2015;91(1):87-92.
- Azhir A, Nasiri J, Ghasari A. Prevalence and Severity of Anemia in Pediatric Hemodialysis Patients; A Single Center Study. *Iran J Pediatr*, 2007;17(1):27-35.
- Madore F, Lowrie EG, Brugnara C, et al. Anemia in hemodialysis patients: Variables affecting this outcome predictor. *J Am Soc Nephrol* 1997;8(12):1921-9.
- Seeherunvong W, Rubio L, Abitbol C, et al. Identification of poor responders to erythropoietin among children undergoing hemodialysis. *The Journal of Pediatrics* 2001;138(5):710–712.
- Ghaderian SB, Mousavi SSB. Relationship between parathyroid hormone and anemia in uremic patients. *Journal of Parathyroid Disease* 2014;2(1):39–40. Available at: <http://www.jparathyroid.com>
- Jung MY, Hwang SY, Hong YA, Oh SY, Seo JH, Lee YM. Optimal hemoglobin level for anemia treatment in a cohort of hemodialysis patients. *Kidney Res Clin Pract* 2015;34(1):20-27.
- Mahdavi-Mazdeh M, Nozari B, Hatmi ZN, Zamyadi M, Mahdavi A. The Impact of Gender and Marital Status on Therapeutic Outcomes of Maintenance Hemodialysis Patients. *Int J Nephrol*

Urol, 2009;1(2):124-128.

34. Meyer TW. Tubular injury in glomerular disease. *Kidney International* 2003;63:774–787.
35. Hayder ZS, Aziz JM, Jaff MS, Effect of Dialysis on Erythropoietin and some Hematological Parameters in Patients with Chronic Renal Failure. *Zanco J Med Sci* 2009;13(2):14-21.
36. Biniiaz V, Tayebi A, Shermeh MS, Abbas E, Nemati E. Prevalence of Functional Iron Deficiency (FID) Anemia in Patients Undergoing Hemodialysis. *Iran J Crit Care Nurs*. 2014;7(1):59-66.
37. Valderrabano F, Horl WH, Maccouqall IC, Rossert J, Rutkowski B. Pre-dialysis survey on anemia management. *Nephrol Dial Transplant*. 2003;18(1):89-100.



Abbreviations list: Analysis of variance (ANOVA), Arteriovenous fistula (AVF), Central venous (CV), Chronic kidney diseases (CKD), Correlation coefficient (r), End-stage renal disease (ESRD), Erythropoietin (EPO), Erythropoietin stimulating agents (ESAs), Femtolitre (f), Gram per decilitre (gm/dl), Haemodialysis (HD), Haemoglobin (Hb), Intravenously (IV), Iron deficiency anaemia (IDA), Left ventricular hypertrophy (LVH), Mean corpuscular haemoglobin concentration (MCHC), Mean corpuscular volume (MCV), Millimole (mmol), Nanogram per millilitre (ng/ml), Non-significant (NS), parathyroid hormone (PTH), Picogram per millilitre (pg/ml), Red blood cells (RBC), Recombinant human erythropoietin (rHuEPO), Serum (s), Standard deviation (SD), Statistical package for social sciences (SPSS), Total Iron Binding capacity (TIBC), Transferrin saturation (TSAT).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this study a part from self funding.

Information – seeking behaviour of primary health care physicians: A sample from Al-Rusafa Health Directorate in Baghdad in 2019

Wesam Abd Al-Reeda Akar,¹ Abdul Ghani Saadoon Hamdan,² Hider Hasan Rahma³

ABSTRACT

INTRODUCTION: Primary health care physicians are the first to face patients' specific problems of all medical specialties. This might trigger the physicians to seek medical knowledge. To find an answer, they may consult colleagues, text books, professional journals, and recently through electronic resources.

OBJECTIVE: To determine medical information-seeking behaviour among primary care physicians at Baghdad Al- Rusafa Health Directorate.

METHODS: A descriptive cross – sectional study was conducted at the Primary Healthcare Centres at Baghdad Al- Rusafa Health Directorate from May till November 2019. Pre- tested self-administered semi structured questionnaire was distributed among four hundred sixty-five physicians working in (96) primary health care centres at Baghdad Al-Rusafa Health Directorate.

RESULTS: the respondent's rate was 67% (312 out of 465) the majority of the participants 188(60.3%) were female physicians. The age of respondents was more than thirty years old 257 (82.4%). Electronic resources was the primary source of knowledge in 200 physicians (64.1%) and solving specific patient problems as a motivated factor to seek information was reported by 161 (51.6%). Also, 181 physicians (58.01%) have reported that they seek medical information on weekly bases.

CONCLUSION: Internet is vital information source that provide health professional with numerous information resources to meet urgent need & answers to patient cases.

Key words: information need, information seeking behaviour, physicians, primary healthcare centre.

INTRODUCTION

Information seeking behaviour is "the purposive seeking for information as a consequence of a need to satisfy some goal".¹ In the last twenty- five years, research has contributed to a better understanding of information need and information seeking behaviour among health practitioners in primary care setting.² because the primary care is vital to any health system, it can deliver significant value if done well³ and researches show that strong primary care is associated with good outcome and lower costs.⁴

Also the primary health care physicians are the providers most patient see first when they have health problem, and the one's they see most often.⁵ So, general practitioners (GP)

occupy a position of pivotal importance in the primary care,⁶ and it is vital that information provision meet the priorities and preference of them.⁷ GPs make decision on how to treat the vast majority of all health related problem in the society, including who should be referred to more comprehensive investigation or treatment.⁸

In addition, keeping the medical knowledge update to cope with the information overload is a major challenge in all branches of medicine.⁹

During physicians' professional workdays, many clinically important patient care questions arise¹⁰ triggering primary healthcare physicians to access a variety of information resources to inform decision-making. Traditional

¹ MBCHB. Medical Educationist. Department of Training and Human Development, Al-Rusafa Health Directorate, Baghdad, Iraq.

² MBCHB. Medical educationist. General Director of Al-Rusafa Health Directorate, Baghdad, Iraq.

³ MBCHB. Statistician at Directorate of Planning and Human Development, Ministry of Health, Baghdad / Iraq.

Corresponding Author: Wesam Abd Al-Reeda Akar, Department of Training and Human Development, Al-Rusafa Health Directorate, Baghdad, Iraq. **E mail:** drwesamedu2020@gmail.com.

resources of health information for health care professionals included printed materials, such as textbooks, clinical manuals, journals drug reference books.¹¹

Studies from low income countries showed that colleagues remained the major source of medical information for health professionals,^{12,13} because they are available, affordable, and reliable.¹⁴ In Iraq, a study in 2014 on physicians working at primary healthcare centres (PHCs) in Al-Karkh district of Baghdad stated that physicians seek medical information primarily from printed textbooks.¹⁵ It seems that physicians prefer to use a certain information source according to its accessibility rather than the quality of the source.¹⁶ The problem with the print resources is that they are out of date by time they are published, they are not always evidence-based, and they are often more academic than practical in their purpose. This is almost the exact opposite of what health care professionals need from knowledge resource. The evidence is clear that health care professionals want and need resources that are continually updated, evidence based and practical.¹⁷

With the development of technology, the practice has started to change through the years. The advent of Internet have given rise to the exponential growth of health information resources which has invariably provided a wider means of access to health professional in meeting their immediate information needs.¹⁸ Electronic resources contain a range of information from primary studies that can be found in journals to synthesized sources including electronic books and synopses of research-based publication.¹⁹

After studying the information seeking behaviour of healthcare physicians in Al-Karkh district of Baghdad 5 years ago,¹⁵ we try this time to measure the change in this behaviour over these years especially after the relative improvement in the availability of the internet service in Iraq. So, the objectives of the study was to measure the common source Iraqi Primary healthcare physicians working at PHCs in Al-Rusafa in Baghdad used to seek medical knowledge and their triggers and frequency to search. In addition to find the barriers and obstacles to this attitude. Also, to test the presence of association between some demographic factors and these variables.

METHODS

Settings and study design: A descriptive cross-sectional study was conducted at primary healthcare centres in Al-Rusafa Health Directorate in Baghdad from 1st May till end of November 2019.

Ethical consideration: The study was approved by the research committee of the Al-Rusafa Health Directorate and implemented according the code of ethics in research of Ministry of Health in Iraq. Verbal consent was taken from all participants after explaining the aims and benefits of the study. All data were kept confidential and used only for the purpose of this study.

Definition of the participants and exclusion criteria: The participants were physicians working at 96 PHCs of the seven central primary healthcare sectors of all ages and both genders. We excluded only those who refuse to participate. .

Sampling: We included PHCs of the seven central primary healthcare sectors at Al-Rusafa Health Directorate: Al- Adhamiya, Al-Sha'ab, Baghdad Al-Jadida, Al-Sader, Al- Baladiyat Al-Awel, Al-Rusafa, and Al-Baladiyat Al-Thani. The PHCs of the three peripheral primary health sectors (Al-Madain, Al-Estiqal and Al-Nahrawan) were excluded from this study due to difficulties in visiting them and limitation of time. We planned a schedule to visit all PHCs in predefined dates. The physicians working at each PHC who were happened to be available at time of visiting this centre were only included in this study.

Study variables: Study variables: The following independent variables age, gender, professional speciality (family senior physician, family permanent doctor, general practitioner and other speciality), and years of work experience (≥ 5 years and < 5 years) were measured and analysed. The following dependent variables were also identified and analysed: the sources of information seeking by the physicians, factors activate and inhibit information seeking behaviour of the physicians, and frequency of information searched by physicians.

Tools: A quantitative close ended questionnaire which was developed by the authors after relevant literature review was used to

take the data from the participants. It was discussed and revised by four assistant professors in the Department of Community Medicine at Al-Kindy College of Medicine and two senior medical educationists.

The questionnaire form has included some demographic characteristics of the physicians participated in the study (age, gender, professional speciality and years of work experience); in addition to four themes in which **theme 1**: covered the sources of medical information used by the physicians, **theme 2**: covered factors triggering physicians to seek medical information, **theme 3**: covered barriers that inhibit physicians to seek medical information, **theme 4**: covered the frequency of searching information by physicians. To assess the understandability of the questions by the participants, we tested the questionnaire on 15 participants without including the results in the final analysis.

The authors have contacted the persons who were responsible for continuous medical education (CME) credits in the all seven primary healthcare sectors. We explained for them the objectives of this study, the targeted doctors needed to be involved, and meaning of the questions in the questionnaire and how to fill them. Those persons were asked to distribute the questionnaire among the potential participants and to explain for them how to fill in the forms. The questionnaires were recollected within a week. The process of data collection was continued from 20th June to 28th July. The questionnaire forms were distributed among 465 physicians who were fulfilling the inclusion criteria of participation, their numbers and response rate in each healthcare sector is shown in **table 1**.

Statistical analysis: Using the SPSS version 24, data were tabulated to measure the frequency and percentages of the variables. Then we tried to find any association between preferred source of information, trigger to search and its frequency, and the barrier and obstacle to search and some demographic features (age, gender, speciality and years of work experience). To measure the statistical significance for any association, we used the Chi square to calculate p value for categorical variables. P value of less than 0.5 was considered statistically non-significant.

Table 1 | The respondents' rate of each PH district

PHC Districts included in the study	Questionnaire distributed	Questionnaire return	Respondent Rate
Al-Baladiyat Al-Awal	50	38	88%
Al- Sader	100	85	85%
Al- Sha'ab	60	41	68%
Al- Adhamiya	75	47	63%
Al- Baladiyat Al-Thani	65	40	62%
Baghdad Al-Jadida	50	30	60%
Al-Rusafa	65	31	48%
Total	465	312	67%

RESULTS

We distributed 456 questionnaire forms, 379 were returned. Of those 312 (68.57 %) were completed and analysed in this study. Most of the respondents 188 (60.3 %) were female physicians, while 124 (39.7 %) were male. Most of them 257 (82.4%) were more than thirty years old, and 258 (82.7%) had five years and more of work experience, with a mean age of 39.4 ± 10.2 .

Regarding profession, the majority of the respondents 130 (41.7 %) were general practitioners, family medicine permanents 41 (13.1%), while family medicine specialist 60 (19.2%) and physicians with Diploma degree in paediatrics, gynaecology, dermatology, rheumatology, internal medicine and post-graduate internships' doctors were 81 (26%) as shown in **table 2**.

Table 3 shows the primary sources used by the participants. It shows that the electronic

Table 2 | Demographic characteristics of physicians participated in the study (no. = 312)

Characteristic	No.	%
Age	< 30	55 17.6
	≥ 30	257 82.4
Gender	Male	124 39.7
	Female	188 60.3
Professional Speciality	General Practitioner	130 41.7
	Family medicine Specialist	60 19.2
	Family medicine permanent	41 13.1
	Other specialities*	81 26.0
Work experience	< 5 years	54 17.3
	≥ 5 years	258 82.7

* Physicians with diploma degree in paediatrics, gynaecology, dermatology, rheumatology, internal medicine and postgraduate internships' doctors

Table 3 | Distribution of study sample according to their primary medical information resources †

	Variable	Printed text-books	Electronic resources	Printed journals	Friends/colleagues	Others*
Gender	Male	61(37.8%)	81(40.5%)	11(57.9%)	19(47.5%)	2(50%)
	Female	100 (62.1%)	119(59.5%)	8(42.1%)	21 (52.5%)	2(50%)
	Total	161(51.6%)	200 (64.1%)	19 (6%)	40(12.8%)	4
	P- value	0.56	0.80	0.14	0.30	0.65
Age	< 30 years	30(18.6%)	33 (16.5 %)	4(21%)	15(37.5%)	1(25%)
	≥ 30 years	131(81.3%)	167(83.5 %)	15(78.9%)	25(62.5%)	3(75%)
	Total	161	200	19	40	4
	P- value	0.65	0.53	0.75	0.001	0.54
Professional Speciality	General practitioner	58 (36%)	78 (39%)	8 (42.1%)	18 (45%)	2
	FM permanents	23 (14.2%)	25 (12.5%)	2(10.5%)	3 (7.5%)	0
	FM specialist	33 (20.5%)	40 (20%)	4(21%)	2(5%)	2
	Other Specialities	47 (29.1%)	57 (28.5%)	5(26.3%)	17 (42.5%)	0
	Total	161	200	19	40	4
	P- value	0.02	0.43	0.98	0.01	0.20
Work experience	< 5 years	27 (16.7%)	32 (16%)	4 (21%)	15 (37.5%)	1
	≥ 5 years	134 (83.2%)	168 (84%)	15 (78.9%)	25 (62.5%)	3
	Total	161	200	19	40	4
	P- value	0.88	0.43	0.75	0.001	0.54

* Included CME activity, printed pamphlets, personal experience, and printed thesis/ dissertation.

† Participants can choose more than one source.

sources are the commonest used 200 (64.1%), also the table shows the association of the type of source used for information seeking and some demographic features.

Table 4 shows the reasons that trigger the primary care physician to seek medical information with the association of these reasons to some demographic features. Specific patient problem is reported in 161(51.6 %) followed by

Table 4 | Distribution of study sample according to the reasons of searching for medical information †

	Variable	Specific patient problem	Update knowledge about disease & health technology	Academic reason	Other reasons
Gender	Male	64 (39.7%)	65 (40.6%)	2(50%)	11(40.7%)
	Female	97 (60.2%)	95 (59.3%)	2 (50%)	16(59.2%)
	Total	161(51.6%)	160(51.2%)	4(1.2%)	27(8.6%)
	P- value	0.99	0.83	0.67	0.91
Age	< 30 years	130 (80.7%)	140 (87.5%)	4(100%)	22(81.4%)
	≥ 30 years	31 (19.2%)	20 (12.5%)	/	5(18.5%)
	Total	161	160	4	27
	P- value	0.43	0.01	0.35	0.89
Professional Speciality	General practitioner	66 (40.9%)	61 (38.1%)	1(25%)	12(44.4%)
	FM permanents	30 (18.6%)	39(24.3%)	1(25%)	4(14.8%)
	FM specialist	17 (10.5%)	29(18.1%)	2(50%)	2(7.4%)
	Other Specialities	48(29.8%)	31(19.3%)	/	9(33.3%)
	Total	161	160	4	27
	P- value	0.29	0.001	0.29	0.63
Work experience	< 5 years	130(80.7%)	143(89.4%)	4(100%)	22(81.4%)
	≥ 5 years	31(19.3%)	17 (10.6%)	/	5(18.5%)
	Total	161	160	4	27
	P- value	0.34	0.001	0.35	0.86

† Participants can choose more than one reason.

Table 5 | Distribution of study sample according to their frequency of searching

	Variable	Daily	Weekly	Monthly	Total	p- value
Gender	Male	38(40.8%)	70(38.7%)	16(42.1%)	124	0.894
	Female	55(59.1%)	111(61.3%)	22(57.9%)	188	
	Total	93	181	38	312	
Age	< 30 years	68(73.1%)	155(85.6%)	34(89.5%)	257	0.017
	≥ 30 years	25(26.8%)	26(14.4%)	4(10.5%)	55	
	Total	93	181	38	312	
Professional Speciality	General practitioner	39(41.9%)	75(41.4%)	16(42.1%)	130	0.082
	FM permanents	12(12.9%)	21(11.6%)	8(21%)	41	
	FM specialist	13(13.9%)	36(19.8%)	11(28.9%)	60	
	Other Specialities	29(31.1%)	49(27%)	3(7.9%)	81	
	Total	93	181	38	312	
Work experience	< 5 years	69(74.1%)	154(85%)	35(92.1%)	258	0.021
	≥ 5 years	24(25.8%)	27(14.9%)	3(7.9%)	54	
	Total	93	181	38	312	

updating knowledge in 160 (51.2 %).

The majority of the participants searching for information on weekly bases in 181 participants (58.01%) and on daily bases in 93 participants (29.8 %). Age and work of experience were significantly associated with the frequency of searching information, p value were 0.017 and 0.021 respectively. **See table 5**

Table 6 shows the barriers and obstacles that the participants reported to affect their information seeking behaviour. The majority, 196 participants (62.8 %), have agreed that the primary barrier against seeking information was inadequate time. Majority of the participants are either accessing the internet at home only or at both home and work, 133(42.6%) and 174(55.7%). **See table 7**

Table 6 | The barriers and obstacles that the participants reported to affect their information seeking behaviour. †

	Variable	Inadequate time	Frequent power cuts	Unreliable information resources of Internet	Poor ICT infrastructure	Personal perception toward internet information	Lack of skill on how to search health information	Lack of access to a computer
Gender	Male	74(37.7%)	16(48.5%)	21(36.8%)	16(50%)	7(58.3%)	4(44.4%)	2(66.6%)
	Female	122(62.2%)	17(51.5%)	36(63.1%)	16(50%)	5(41.6%)	5(55.5%)	1(33.3%)
	Total	196	33	57	32	12	9	3
	P- value	0.35	0.27	0.62	0.21	0.18	0.77	0.33
Age	< 30 years	162(82.6%)	28(84.8%)	15(26.3%)	4(12.5%)	11(91.6%)	3(33.3%)	1(33.3%)
	≥ 30 years	34(17.3%)	5(15.1%)	42(73.6%)	28(87.5%)	1(8.3%)	6(66.6%)	2(66.6%)
	Total	196	33	57	32	12	9	3
	P- value	0.35	0.27	0.62	0.21	0.18	0.77	0.33
Professional Speciality	General practitioner	77(39.3%)	16(48.5%)	21(36.8%)	18(56.2%)	5(41.6%)	4(44.4%)	2(66.6%)
	FM permanents	44(22.4%)	4(12.1%)	8(14%)	4(12.5%)	0	0	0
	FM specialist	23(11.7%)	4(12.1%)	6(10.5%)	5(15.6%)	2(16.6%)	3(33.3%)	0
	Other Specialities	52(26.5%)	9(27.2%)	22(38.5%)	5(15.6%)	5(41.6%)	2(22.2%)	1(33.3%)
	Total	196	33	57	32	12	9	3
	P- value	0.22	0.69	0.11	0.23	0.29	0.19	0.68
Work experience	< 5 years	162(82.6%)	27(81.8%)	43(75.4%)	29(90.6%)	11(91.6%)	6(66.6%)	2(66.6%)
	≥ 5 years	34(17.3%)	6(18.1%)	14(24.5%)	3 (9.3%)	1(8.3%)	3(33.3%)	1(33.3%)
	Total	196	33	57	32	12	9	3
	P- value	0.98	0.88	0.15	0.21	0.40	0.19	0.46

† Participants can choose more than one cause.

Table 7 | Availability and access to computer with Internet

	Variable	At home	At work	Both	Total	p- value
Gender	Male	50(37.6%)	3(60%)	71(40.8%)	124(39.7%)	0.55
	Female	83(62.4%)	2(40%)	103(59.2%)	188(60.3%)	
	Total	133(42.6%)	5(1.6%)	174(55.7%)	312	
Age	< 30 years	106(79.7%)	4(80%)	147(84.5%)	257(82.4%)	0.54
	≥ 30 years	27(20.3%)	1(20%)	27(15.5%)	55(17.6%)	
	Total	133(42.6%)	5(1.6%)	174(55.7%)	312	
Professional Speciality	General practitioner	54(40.6%)	3(60%)	73(41.9%)	130(41.6%)	0.57
	FM permanents	30(22.5%)	/	30(17.2%)	41(13.1%)	
	FM specialist	13(9.7%)	1(20%)	27(15.5%)	60(19.2%)	
	Other Specialities	36(27.1%)	1(20%)	44(25.3%)	81(25.9%)	
	Total	133(42.6%)	5(1.6%)	174(55.7%)	312	
Work experience	< 5 years	106(79.7%)	5(100%)	147(84.5%)	258(82.7%)	0.32
	≥ 5 years	27(20.3%)	/	27(15.5%)	54(17.3%)	
	Total	133(42.6%)	5(1.6%)	174(55.7%)	312	

DISCUSSION

Preference of information source: The advent of Internet has given rise to the exponential growth of health information resources which has invariably provided wider means of access to health professional in meeting their immediate information needs.^{18,20}

In the present study, primary healthcare physicians preferred electronic resources 200 (64.1%) as their primary information source. In a similar study¹⁵ conducted in Al-Karkh Health Directorate in Baghdad in 2014 on the same target of physicians, 114 (43.8 %) stated that printed texts were the primary source for information seeking while only 71 (27.3 %) of the participants were preferring electronic sources. This dramatic change may be due to the change in the attitude of physicians working at the primary healthcare centres and the better internet infrastructure in the country.

Many other studies have shown also that electronic resources are the primary source of information seeking behaviour: Kostagiolas²¹ on hospital professionals in Greece, Oriogu¹⁸ on health professional in Federal Medical Center in Abuja in Nigeria, Perera²² on health related academics from University of Peradeniya in Sri Lanka, and Grefsheim et al² on scientists and science administrators from US National Institutes of Health. However, Andualem²³ from Ethiopia in 2012, Graber,²⁴ Coumou⁴ in his review on published papers from 1992-2005, and Bryant⁷ in 1999 on family

physician in UK have shown that colleagues or paper sources are more used for information seeking. The reasons for this discrepancy in the attitude are most of these studies were done in 1990s and early 2000s where online resource were not widely distributed and available, poor infrastructures of internet, physicians' believe that sources other than electronic are easier and more efficient.²⁵

The present study showed that most of the participants have accessed the Internet at home 133 (42.6%), office 5(1.6%), or both 174 (55.7%) this result is similar to that of Gonzalez¹⁶ study on Spanish primary care physicians where 72% of them have no Internet at their offices.

Frequency of information use: During patient consultation, primary care physicians need patient-specific information. Accessing information in a timely way is essential for the clinical decision- making process.²⁶

The present study showed that most of physicians 181 (58%) search for medical information on weekly basis, while 93 (29.8%), 38 (12.1%) on daily and monthly basis respectively. This result was consistent with that of Cook et al²⁷ where he showed that primary healthcare and subspecialist internal and family physicians use one or more online reference at least twice weekly, Bennett 2005,⁷ and Jette et al⁸ from Norway in 2016.

This frequent tendency of the primary healthcare physicians to seek medical infor-

mation is because they face particular challenges in keeping updated. They usually meet patient with undifferentiated problems and need regular and systematic updated in all field of medicine at satisfactory level. In addition to work in a small unit or a single-handed outside teaching environment and without an organized peer review setting.⁸

The present study identified a statistically significant direct association between the frequency of searching for medical information with age of the physicians (p- value 0.017) and their years of work experience for more than five years, p- value 0.021. This may be due to their professional responsibilities toward their patients or more need with age to update knowledge with relevant information for the sake of the population who use primary health care facilities.²⁰ In addition, with age physician becomes well known from their patients so expanding and updating knowledge will lead to provide a high-quality health services and avoid as much as possible medical errors.

Trigger to seek medical information: The present study showed that most physicians 161 (51.6%) seek medical information to solve a specific patient problem and this result was consistent with the study of Bryant⁷ on general practitioners in Aylesbury Vale in the UK, Bennett in 2002-2003 on US physician of all specialties,²⁷ Soel et al on academic physician in Colombia University in USA in 2004,²⁸ and Gorman in his study on non-academic primary health care physicians in USA.²⁹

Other studies have stated that the commonest cause physicians find to search medical information is improving social and communication skill as in Kostagiolas,²¹ conducting research and writing articles as in Perera,²² or just updating their knowledge as in Norbet from Tanzania.¹⁴

These differences in setting the causes that may trigger physicians to seek medical knowledge may be attributed to the diversity of the targeted physicians: academic or non-academic, general or specialist, working at PHCs or in hospitals. In addition to the effect of socio-cultural differences.

Barriers to seek medical information physicians': Physicians have many information needs that arise at the point of care yet go unmet for a variety of reasons.³⁰ The present

study showed that lack of time 196 (62.8%) was the major obstacles to search for information. This result was consistent with Kostagiolas²¹ study and Coumou et al.⁴ Ely in a study conducted in Iowa in the USA and published in 2005³¹ has shown that the major barrier of their studied respondent was the doubt about the existence of relevant information followed by lack of time.

The limitation of this study was our inability to expand the study to include more healthcare sectors in Baghdad Al-Rusafa and to include other healthcare providers like dentists, pharmacists, and nurses.

CONCLUSION

The Primary healthcare physicians working in the central PHCs in Al-Rusafa find that they should seek medical information at least once weekly triggered by a specific patient problem then tendency to Update knowledge about disease and health technology. The most common source used by the PHC physicians to seek for medical knowledge was the electronic resources followed by printed textbooks. Lack of time was the major obstacle to seek for medical information in primary care physicians.

REFERENCES

1. Wilson TD. Human Information Behavior. *Informing Science* 2000; 3(2):49-55.
2. Grefsheim SF, Rankin JA. Information need and Information Seeking in a biomedical research setting: a study of scientists and science administrators. *J Med Libr Assoc* 2007; 95(4):426-434.
3. Schoen C, Osborn R, Doty M, Squires D, Peugh J. A survey of primary care physicians in Eleven Countries, 2009: Perspectives on Care, Costs, and Experiences. *Health Aff* 2009;28(6): 1171- 1183. Available at www.ncbi.nlm.nih.gov/pubmed/19884491
4. Coumou HC, Meijman FJ. How do primary care physicians seek answers to clinical questions? A literature review. *J Med Libr Assoc* 2006; 94(1):55-60.
5. World Health Organization Regional Office for South – East Asia: Regional Consultation on Strengthening the Role of Family /Community Physicians in Primary Health Care. 2011; Jakarta, Indonesia,19-21 October
6. Fountaine T, Richardson B, Wilson F. How to improve clinical behavior in primary care. *Health International* 2012; 12 available at: <http://healthcare.mckinsey.com>
7. Bryant SL. The information needs and Information seeking

- behavior of family doctors. Health Libraries Group. *Health Information and Libraries Journal* 2004; 21(2):84-93.
8. Le JV, Pedersen LB, Riisgaard H, Lykkegaard J, Nexøe J, Lemmergaard J et al : Variation in general Practitioners' information – seeking behavior- across sectional study on the influence of gender, age, and practice form. *Scandinavian Journal of primary Health Care* 2016; 34(4): 327-335.
 9. Aasland OG, Nylenna M. Primary care physicians & their information – seeking behavior. *Scand J prim health care* 2000; 18(1):9-13.
 10. D'Alessandro D M. Kreiter CD, Peterson MW. An Evaluation of Information – seeking Behaviors of General Pediatricians. *PEDIATRICS* 2004;113(1):64-69.Doi: 10.1542/peds.113.1.64.
 11. Dawes M, Sampson U. Knowledge management in clinical practice: a systemic review of information seeking behavior in physicians. *International Journal of Medical Informatics* 2003; 71(1):9-15.
 12. Tumwikirize WA, Ogwal-Okeng JW, Vernby A, Anokbonggo WW, Gustafsson, Lundborg CL. Access & use of medicines information sources by physicians in public hospital in Uganda: across sectional survey. *African Health Sciences* 2008; 8(4):220- 226.
 13. Martinez – silverira MS, Oddone N. Information seeking behavior of medical residents in clinical practice in Bahia, Brazil. *J Med Libr. Assoc* 2008; 96(4):381-384.
 14. Norbert GL. Lwoga ET. Information – seeking behavior of physicians in Tanzania. *Information Development* 2013;29(2):1-12.
 15. Abdul Reeda W, Al- Musawi M. Seeking behavior for medical information among physicians of the primary health care centers in Baghdad AL- Karkh in Iraq. *Iraqi new medical journal* 2019; 5(9):28-34.
 16. González-González AI, Dawes M, Sánchez-Mateos J, Riesgo-Fuertes R, Escortell-Mayor E, Sanz-Cuesta T and Hernández-Fernández T. Information Need and Information – Seeking Behavior of Primary Care Physicians. *Annals of Family Medicine* 2007; 5(4):345-352.
 17. Walsh K, Bhagavatheeswaran L. The future of continuing professional development. *Iraqi new medical journal* 2019;5(10):70- 71.
 18. Oriogu CD, Subair RE, Oriogu-Ogbuiyi DC. Use of Internet Health Information Resources and Information Seeking Behavior among Health Professional in Federal Medical Center, Abuja: 2017. *Library philosophy and Practice* 2017. Available at: <http://digitalcommons.unl.edu/libphilprac/1511>
 19. McGowan J, Grad R, Pluye P, Hannes K, Deane K, Labrecque M, Welch V, Tugwell P. Electronic retrieval of health information by health care providers to improve practice & patient care. *Cochrane Database syst rev.*; (3): cd004749.doi: 10.1002/14651858.cd004749.pub2.
 20. Kim GR, Bartlett EL and Lehmann HP. Information resources preferences by general pediatricians in office setting: a qualitative study: *BMC Medical Informatics and Decision Making* 2005;5:34. doi:10.1186/1472-6947-5-34.
 21. Kostagiolas PA, Ziavrou K, Alexias G and Niakas D. studying the Information- Seeking Behavior of Hospital Professionals: the case of METAXA cancer hospital in Greece. *Journal of Hospital librarianship* 2012; 12(1):33-45.
 22. Perera PASH: Preference and Pattern of Information seeking of Academics of Health-Related Faculties, University of Peradeniya (UOP). *Journal of the University Librarians Association of Sri Lanka* 2014;18(2):62-75.
 23. Andualem M, Kebede G, Kumie A. Information needs and seeking behavior among health professionals working at public hospital and health centers in Bahir Dar, Ethiopia. *BMC Health Services Research* 2013; 13(1):534. <https://doi.org/10.1186/1472-6963-13-534>
 24. Graber MA, Randles BD, Monahan J, Ely JW, Jennissen C, Peters B, Anderson D. What questions about patient care do physicians have during and after patient contact in the ED? The taxonomy of gaps in physician knowledge. *Emerg Med J* 2007;24(10):703- 706.
 25. Davies K. The information- seeking behavior of doctors: a review of the evidence. *Health Information & Libraries Journal* 2007; 24:78-94.
 26. Clarke MA, Belden JL, Koopman RJ, Steege LM, Moore JL, Canfield SM, Kim MS. Information needs and information seeking behaviour analysis of primary care physicians and nurses: a literature review. *Health Information and Libraries Journal* 2013;30(3):178-90.
 27. Bennett NL, Casebeer LL, Kristofco R, Collins BC: Family physicians' information seeking behaviors: a survey comparison with other specialty. *BMC Medical Informatics & Decision Making* 2005;5:9. Available at: <https://doi.org/10.1186/1472-6947-5-9>
 28. Seol YH, Kaufman DR, et al: Scenario – based Assessment of physicians' Information Needs. Available at www.ncbi.nlm.nih.gov/pubmed/15360824
 29. Gorman PN. Information needs in primary care: a survey of rural & non rural primary care physicians. *MEDINFO* 2001;10(1):338-342.
 30. Maggio LA, Cate OT, Moorhead LL, Stiphout FV, Kramer BMR, Edith ter Braak ET, et al. Characterizing physicians' information needs at the point of care. *Perspect Med Educ* 2014;3:332- 342
 31. Ely JW, Osheroff JA, Chambliss ML, Ebell MH, Rosenbaum ME. Answering Physicians' Clinical Questions: Obstacles and Potential Solution'. *Journal of the American Medical Informatics Association* 2005;12(2):217-224.



Abbreviations list: Continuous medical education (CME), Family Medicine (FM), General practitioners (GP), Information and communication technology (ICT), Number (no.), Primary healthcare (PH), Primary healthcare centres (PHCs), Statistical package for social sciences (SPSS), United State of America (USA).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this study a part from self funding.

Drug compliance of patients with hypertension and/or type II diabetes mellitus: a sample from PHCs in Al-Resafa, Baghdad, 2018

Sahar A E Al Shatari,¹ Sally A Witwit,² Khelowd Salih,³ Yahiya B H Al- Juboori,⁴ Ahmed Sabbar Gabur,⁵ AlaaSafaa Abed,⁶ Shams Wisam Talib Al-Tabtabae,⁷

ABSTRACT

INTRODUCTION: Hypertension and type 2 diabetes mellitus are common chronic diseases in the community. Patient compliance to drugs is a factor in the positive outcome of medical treatment.

OBJECTIVE: To measure drug compliance of patients with hypertension and/or type 2 diabetes mellitus visiting primary healthcare centres (PHCs), and to find an association between the level of compliance and some epidemiological factors.

METHODS: A cross sectional study with analytic element was conducted at Al-Resafa health Directorate in the first half of 2018. The targets were patients with hypertension and/or type 1 diabetes mellitus who are visiting six PHCs in Al-Resafa district in Baghdad. Drug compliance were measure by Morisky compliance scale, Pill identification test, and tablet account and then overall compliance were measure from them. Association of level of compliance with age, gender, level of education, marital status, tendency of the patient to visit other health care institutes, having health education, level of communication with healthcare providers and implication of life style modification was studied.

RESULTS: Of 300 patients enrolled, 148 patients had hypertension, 76 had type 2 diabetes mellitus, and 76 have both. Most of patients, 103(34.3%), were aged between 50-59 years. By Morisky scale 113 patients (38.43%) showed low drug compliance; however, by tablet accounts and pills identification 221 patients (75.17%) and 264 patients (89.79%) showed good drug adherence respectively. The overall good compliance was reported in 108 patients (36.73%). The level of compliance by overall scale is significantly associated with the patient's attitude to visit health institutions other than PHCCs and the effectiveness of patient-health care providers' communication.

CONCLUSION: Pill identification test shows the highest rate of good drugs complaints while Morisky scale shows the lowest. In general compliance is still poor and by overall compliance scale about two thirds of patients were incompliant.

Key words: hypertension, type 2 diabetes mellitus, drug compliance, Morisky scale, Pill identification test, tablet account.

INTRODUCTION

Non-communicable diseases are chronic in nature and may be incurable; however, early detection and proper management of such diseases can reduce morbidity and premature death and may improve the quality of life.¹ Hypertension and diabetes mellitus are good examples for these chronic diseases.

Hypertension (HT) is a major public-health challenge worldwide because of its high prevalence and concomitant risks of cardiovascular, cerebral and kidney diseases, as well as being the leading risk factor for mortality and disability globally. It affects over one billion people, and one in every three adults, whom has high blood pressure; had poor or noncompliance produce uncontrolled hypertension that will lead to more complications.²

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic disorder,³ and its global

¹ MBCHB. FICMS. Consultant Family Physician, Training PHC Centre for Family Health Approach at Bab Al-Moatham, Baghdad, Iraq.

² MBCHB. FICMS. Department of Non-Communicable Diseases, Public Health Directorate, MoH, Baghdad, Iraq.

³ MBCHB. DFM. Family Physician, Training PHC Centre for Family Health Approach at Bab Al-Moatham, Baghdad / Iraq.

⁴ MBCHB. FICMS. Al-Edresi PHC, Al-Resafa Health Directorate, Baghdad, Iraq.

⁵ MBCHB. Fakher Aldeen Al-Jameel PHC, Al-Resafa Health Directorate, Baghdad, Iraq.

⁶ MBCHB. FICMS. Al-Resafa District for Primary Health, Al-Resafa Health Directorate, Baghdad / Iraq.

⁷ MBCHB. FICMS. Al-Zewaia PHC, Al-Resafa Health Directorate, Baghdad / Iraq.

Corresponding Author: Sahar A E Al Shatari, Training PHC Centre for Family Health Approach at Bab Al-Moatham, Baghdad, Iraq. E mail: saharissa2020@yahoo.com

estimated prevalence will increase from 6.9 % in 2010 to 7.7 % in 2030.⁴ The goals of care for patients with type 2 diabetes mellitus are to eliminate symptoms and to prevent, or at least slow, the development of complications. Micro vascular (i.e. eye and kidney disease) and Macro vascular (i.e. coronary, cerebrovascular, peripheral vascular) risk reduction is accomplished through control of blood sugar.⁵

Glycemic control largely depends on compliance with medication therapies. In fact, the most common problem in patients with diabetes is non-compliance with medications.^{6,7} WHO Adherence meeting in June 2001¹ defined adherence as “the extent to which the patient follows medical instructions”. A number of rigorous reviews have found that, in developed countries, adherence among patients suffering chronic diseases averages only 50%. This is assumed to be even higher in developing countries given the paucity of health resources and inequity in access to health care.⁸ Many factors are involved in patient non-adherence : factors related to the characteristics of the disease, medication side effects, duration of treatment, frequency of expected intake, complexity of treatment, and severity of the disease.⁹

Drug compliance is very important topic and has been studied many times nationally and internationally; however, the results are diverse depending on the scale used to measure the compliance, the target of patients involved in the study, and some other sociocultural factors related to each community. In this study we aimed at measuring the compliance of Iraqi patients who are suffering from hypertension and type 2 diabetes mellitus and visiting primary healthcare centres (PHCs) in Al-Resafa district in Baghdad and to find any factors that may associate the level of compliance.

METHODS

Settings and study design: A cross-sectional study with analytic element was conducted at six primary healthcare centres (PHCs) in Al-Resafa Sector: Bab Al-Moadhum, Mustansiriyah, Al-Edresi, Babel, Al-Zewaia, and Fakher Aldeen Al-Jameel. Three hundred patients who already diagnosed with hypertension and/or type 2 Diabetes Mellitus (According to the patient medical records in these PHCs which

based on Iraqi ministry of health guideline and instruction), were involved in this study. The data collection was carried out over 4 months from February to May 2018, while the whole study was conducted from 1st January to 30th June 2018.

Ethical consideration: The study protocol has been approved by the research committee of Al-Resafa Health Directorate in accordance to the code of ethics of Ministry of Health in Iraq. The objectives of the study were explained to all participants and their verbal consent were taken before collecting data that were kept confidential throughout the stages of performing the study.

Definition of the participants and exclusion criteria: in this study, we enrolled patients who had records in the selected PHC and had visited these centres during the studied period and having HT and/or T2DM for at least 6 months before the study. Pregnant ladies and those who refused to participate were excluded from the study. In our PHCs, the hypertension is diagnosed when blood pressure is above 140 and/or > 90 mmHg in two visits separated by at least two weeks.¹⁰ While type 2 DM is diagnosed as a postprandial plasma glucose or blood capillary sugar of more than 200 mg/dl, Fasting plasma glucose of ≥ 126 mg/dl, or HbA1c measurement $\geq 6.5\%$.¹¹

Sampling: We use the convenient sampling in enrolment of patients in this study because of limited time and resources.

Tools: The questionnaire form to extract the data was modified from the Rational Pharmaceutical Management plus Program.¹¹ The questionnaire form has been prepared and translated by researchers then it has been revised by eleven experts; 3 community physicians, 5 family physicians, and 3 internal physicians. The questionnaire form was tested by a pilot study on 30 patients whom have not been involved in the final analysis of the study.

Outcomes and procedures: First, we assessed the level of compliance for using drugs by three scales; Morisky compliance scale, tablet accounts, and pill identification test (PIT). Then we calculated the overall compliance. Each were grouped into three categories good compliance, medium compliance, and low compliance.

Morisky compliance scale¹² also known as self-report scale has consisted of 8 items each given one score. Eight score means good compliance, 6-7 score means medium compliance, and less than 6 score means low compliance. The percent of tablet accounts were calculated as follow:

Table accounts %= [giving tablets-remaining tablets]/ tablets must be taken] x 100%

The compliance is good when the accounts is 95 % and above, medium when it is 75-94 %, and low when it is less than 75%. Pill identification test¹³ depends on the ability of the patient to know the dose of the drug, time of taking the drug, and additional instructions about it. If the patient answers these three questions correctly, it would be designated as a good drug compliant; answers correctly only the questions about the dose of the drugs and their time of administration, it would be designated as a medium compliant; and answers correctly only one question or confuses to answer anyone then the compliance is labelled as being low.

The overall compliance approach provides data from different scales. This can overcome some drawbacks in each scale for example Morisky scale (self-reporting) overestimates the compliance.⁹ We tabulated the data from different scales as seen in **table 1**. If data fall in the same vertical column are harmonized in terms of level of compliance, the overall compliance would be good if all the three scale are good, medium if all of them are medium, and low if all of them are low. If data of a similar level of compliance of the three scales distributed over two columns, we take the right column as the estimated adherence. While if they spread over the three columns then we use the middle level of adherence.

After that, we try to find any association between some parameters and the degree of compliance. The parameter tested were age, gender, level of education, current marital status, visiting public and/ or private health institutions, level of health education received by the patients, degree of communication level with

health care providers, and complying with the life style modification related to his diseases.

Level of health education was assessed based on the American Family Physician Guidelines.¹⁵ It based on the ability of the patient to know some of the risk factors about his disease like quitting smoking, switching from saturated to unsaturated fat, doing regular exercise, decreasing salt intake, drinking purified water. If all the five items are done by the patient it considered good health education, if 3-4 items are done it is considered middle health education, and it would be poor if two or less items are done.

Communication between patients and healthcare providers were assessed through answering 8 questions. The first four were about patient's understanding about the disease, its seriousness, its complications and danger, and its drugs and treatment. The second four were about patient's perception whether the health care providers have explained the disease, explained drugs and management, explained cost and benefit, and were very helpful on counselling. Health care providers have included doctors and nurses. We considered communication as being good if answer yes to 5-8 questions, while it is considered weak if the patient answer yes to 4-0 questions.

In order to assess control state for each patient, we measured the blood pressure by a mercury sphygmomanometer after asking the patient to be in complete rest for at least 30 minutes. The first reading is omitted and we took the second one 10 minutes apart. Then, a venous blood sample was withdrawn to measure the random blood sugar. Blood pressure below 140/90 mmHg and random blood sugar less than 180 mg/dl was considered a marker of control. Measurement of HbA1c was not available at the PHCCs at the time of the study.

Statistical analysis: The statistical package for social science (SPSS) version 23 was used for data entry and analysis. Data were presented in simple measures of frequencies,

Table 1 | Over all compliance

Self-reporting (Morisky)	No to all questions	Yes to 1 question	Yes to 2 or more questions
PIT- Client knows the...	Dose, time, and instructions	Dose and time	Dose only or confused
Pill count	95% or more	75–94%	Less than 75%
Overall Adherence	Good or high	Medium or Moderate	Low

Characteristics		Frequency (No. = 300)	%
Age (years)	< 40	21	6.9
	40-49	52	17.3
	50-59	103	34.3
	60-69	89	29.7
	70-79	31	10.3
	≥ 80	4	1.3
Gender	Male	83	27.7
	Female	217	72.3
Educational level	Illiterate	49	16.3
	Can read and write	23	7.7
	Complete primary	100	33.3
	Complete secondary	78	26.0
	Graduate college/institution	47	15.7
	Postgraduate	3	1.0
Marital status	Currently not married	68	19.3
	Currently married	242	80.7
Presence of DM or / and HT	Hypertension	48 / 224 with HT	49.3
	Diabetes Mellitus	76 / 152 with DM	25.3
	Both	76	25.3

percentage; chi-square test for independence was used to test the significance of associations between discrete variable. P value less than 0.05 were considered significant.

RESULTS

In this study, 300 patients agreed to participate, and their mean of age was 57 years $\pm$ 5.083. A third of them 103(34.3%) were in the age group 50-59 years, a majority were women 217 (72.3%), and 148 patients (49.3 %) had only hypertension, 76 (25.3 %) had only diabetes mellitus, and 76 (25.3 %) had both diseases. For other demographic features see **table 2**

Figure 1 shows that about two thirds of patients with HT or T2DM were uncontrolled, 156 patients (69.6 %) for HT and 98 (64.5 %) for T2DM.

Table 3 shows the level of compliance in the three scales and the overall compliance. The pill identification test has shown the highest good compliance 264 (88%). On the contrary, Morisky scale has shown that 113 patients (37.7 %) had low compliance.

Table 4 shows the association of some

parameters to the level of compliance as measured by Morisky scale. The only statistically significant association was with visiting health institutions other than PHCs, p value is 0.033. While it was the understanding of life style modification that found to have a statistically significant association with the level of compliance measured by tablet account (P value 0.000), see **table 5**. **Table 6** shows that assessment of patient- health care providers' communication and understanding life style modification have shown a significant statistical association with the level of compliance where it is measured by pill identification test (P value 0.000 and 0.008 respectively). For the overall compliance (**table 7**), the statistically significant association was with visiting health association other than PHCs (P value 0.004), and the assessment of patient- health care providers' communication (P value 0.031)

DISCUSSION

About two thirds of the respondents were

Type of the scales	Level of compliance	No.	%
Self-report/ Morisky scale	Good compliance	96	32
	Medium compliance	85	28.3
	Low compliance	113	37.7
Pill Identification Test	Good compliance	264	88
	Medium compliance	20	6.7
	Low compliance	10	3.3
Tablet accounts	Good compliance	221	73.3
	Medium compliance	28	8.7
	Low compliance	45	14.7
Over all compliance	Good compliance	89	30.3
	Medium compliance	108	36.7
	Low compliance	97	33
Total		294	100

Note: Analysis was done on 294 patients because 6 were on no drugs

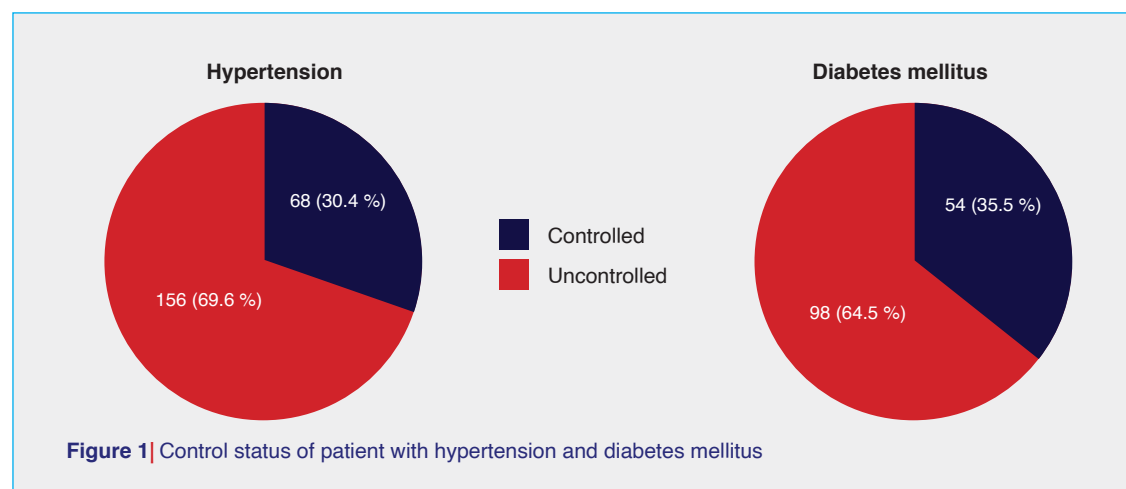


Table 4 | Relationship between studied patients' Morisky compliance scale/self-report and their demographic features PHC services

Characteristics		Self-report (Morisky scale of compliance)			Total N=294	P value
		Good N = 96	Medium N = 85	Low N = 113		
Age (years)	≤ 40	5	5	11	21	0.538
	40-49	18	15	16	49	
	50-59	32	25	44	101	
	60-69	26	30	32	88	
	≥ 70	15	10	10	35	
Gender	Male	26	25	31	82	0.932
	Female	70	60	82	212	
Educational level	Illiterate	19	11	18	48	0.186
	Read and write	10	8	4	22	
	Primary certificate	25	28	45	98	
	Secondary certificate	22	26	29	77	
	College/institution certificate	19	10	17	46	
	Postgraduate certificate	1	2	0	3	
Married condition	Currently not married	17	15	25	57	0.644
	Currently married	79	70	88	237	
Visiting other than PHC	Only go to PHC	17	10	24	51	0.033
	Public health institution	10	25	20	55	
	Private health institution	64	48	63	175	
	Privet and public clinic	5	2	6	13	
Received HE	Received good HE	45	50	46	141	0.063
	Received middle HE	40	32	53	125	
	Received weak/no HE	11	3	14	28	
Assessment of patient-healthcare providers' communication	Good communication	83	80	99	262	0.206
	Weak communication	13	5	14	32	
Life modification	Well bound to life modification	83	75	86	244	0.099
	Weak bound to life modification	13	10	27	50	

Note: Analysis was done on 294 patients because 6 were on no drugs

Table 6 | Level of drug compliance of patients by Pill Identification Test and their association with some demographic features and PHC services.

Characteristics	Pill identification test (compliance)				P value
	Good N= 264	Medium N= 20	Low N=10		
Age (years)					
≤ 40	18	2	1		0.568
40-49	46	2	1		
50-59	92	7	2		
60-69	80	4	4		
≥ 70	28	5	2		
Gender					
Male	75	4	3		0.712
Female	189	16	7		
Educational level					
Illiterate	42	4	2		0.578
Read and write	20	0	2		
Primary certificate	85	10	3		
Secondary certificate	70	4	3		
College/institution certificate	44	2	0		
Postgraduate certificate	3	0	0		
Married condition					
Currently not married	49	5	3		0.538
Currently married	215	15	7		
Visiting other than PHC					
Only go to PHC	44	5	2		0.563
Public health institution	47	4	4		
Private health institution	161	10	4		
Privet and public clinic	12	1	0		
Received HE					
Received good HE	129	8	4		0.736
Received middle HE	111	10	4		
Received weak/no HE	24	2	2		
Assessment of patient-healthcare providers' communication					
Good communication	237	20	5		0.000
Weak communication	27	0	5		
Life style modification					
Well bound to life modification	225	12	7		0.008
Weak bound to life modification	39	8	3		

Note: Analysis was done on 294 patients because 6 were on no drugs

Table 5 | Level of drug compliance of patients by tablet account and their association with some demographic features and PHC services.

Characteristics	Tablet count (compliance)				P value
	Good N= 221	Medium N= 28	Low N=45		
Age (years)					
≤ 40	15	1	5		0.137
40-49	35	9	5		
50-59	73	13	15		
60-69	69	4	15		
≥ 70	29	1	5		
Gender					
Male	60	6	16		0.376
Female	161	22	29		
Educational level					
Illiterate	38	2	8		0.513
Read and write	19	0	3		
Primary certificate	72	9	17		
Secondary certificate	57	9	11		
College/institution certificate	32	8	6		
Postgraduate certificate	3	0	0		
Married condition					
Currently not married	46	4	7		0.555
Currently married	175	24	38		
Visiting other than PHC					
Only go to PHC	35	3	13		0.318
Public health institution	42	4	9		
Private health institution	133	20	22		
Privet and public clinic	11	1	1		
Received HE					
Received good HE	105	13	23		0.904
Received middle HE	96	11	18		
Received weak/no HE	20	4	4		
Assessment of patient-healthcare providers' communication					
Good communication	196	28	38		0.106
Weak communication	25	0	7		
Life modification					
Well bound to life modification	195	21	28		0.000
Weak bound to life modification	26	7	17		

Note: Analysis was done on 294 patients because 6 were on no drugs

Table 7 | Level of drug compliance of patients by over all compliance level and their association with some demographic features and PHC services.

Characteristics		Tablet count (compliance)			P value
		Good N = 89	Medium N = 108	Low N = 97	
Age (years)	≤ 40	4	6	11	0.655
	40-49	17	20	12	
	50-59	31	37	33	
	60-69	25	34	29	
	≥ 70	12	11	12	
Gender	Male	24	30	28	0.958
	Female	65	78	69	
Educational level	Illiterate	17	12	19	0.138
	Read and write	10	8	4	
	Primary certificate	24	35	39	
	Secondary certificate	19	33	25	
	College/institution certificate	18	18	10	
	Postgraduate certificate	1	2	0	
Married condition	Currently not married	15	20	22	0.579
	Currently married	74	88	75	
Visiting other than PHC	Only go to PHC	16	11	24	0.004
	Public health institution	7	27	21	
	Private health institution	61	67	47	
	Privet and public clinic	5	3	5	
Received HE	Received good HE	40	60	41	0.224
	Received middle HE	38	42	45	
	Received weak/no HE	11	6	11	
Assessment of patient- healthcare providers' communication	Good communication	76	103	83	0.031
	Weak communication	13	5	14	
Life modification	Well bound to life modification	78	92	74	0.089
	Weak bound to life modification	26	7	17	

Note: Analysis was done on 294 patients because 6 were on no drugs

aged (50-69) years old; this is expected because the prevalence of hypertension and type 2 diabetes mellitus increases with age. The third NHANES survey reported that the prevalence of hypertension grows significantly with increase age in all gender and race groups.^{11,16,17}

In our data, 217 participants (72.3 %) were women. This is the norm in Iraq as women usually visit PHCs for herself or to bring their children, while men usually work in the morning.¹⁸ Also, this is consistent with non-communicable diseases (NCD) survey in which women tend to seek for advice more than men.^{19,20} In Ghazza, Palestine; women represent 60.8 % of those who registered as having chronic diseases.²¹

About one third of the participants had

completed their primary education and more than three quarters were married at the time of the study. This is consistent with the results of the NCD risk factors STEPS survey in Iraq 2015¹⁹ that estimated the largest percentage of the respondents (25.5%) had completed the primary education and 75% of the respondents were married at time of the survey.

More than 80 % of the participants are visiting health institutes other than PHCs, the majority of those are visiting the private clinics. The reasons behind this attitude may be explained by the lack of some laboratory tests like HbA1c, inconsistent availability of the drugs, low confidence with the quality of services or its prices that are provided by the PHCs, or patients' preference to go directly to the hospitals.

Effective communication between the physician and the patient depends partly on physician's confidence in his/her ability to treat and educate the patients and to the availability of enough time during the daily practice. The vast majority of the participants have thought that they received a good counselling, and high percentage had modified their lifestyle according to doctor's instructions. This is similar to a study conducted in USA in which 84.3% of the adult population reported receiving lifestyle modification counselling.²² As receiving health education about life style modification is important and its one component of management of chronic disease especially T2DM and HT.²³

On assessing the compliance by many scales, we found that good compliance was found in 264 patients (88 %) in pill identification test, and in 221 patients (73.3 %) and 96 patients (32 %) in tablet accounts and Morisky scales respectively. The overall compliance was found in about 30 % of our sample.

The Morisky scale is the closest ratio of good compliance to the overall compliance. The low rate of good compliance in Morisky scale is in contrary to what is known as Morisky scale may overestimate the compliance because the patient might hide some facts regarding use of drugs regularly.⁹

In our study we found that about a third of participants was a good adherent to their medication as measured by Morisky scale, and this is much less than what a Lebanese study²⁴ has shown in patients with hypertension where 50 % of them are highly adherent to their medication according to Morisky scale.

The overall patient's compliance less than one third of the participants showed full adherence. This percentage is a bit higher than the result of a study in Iraq where less than a quarter of surveyed patients with hypertension reported to be full adherent to their medications.^{2, 25} Our good adherence rate was also better than that reported from Ethiopia²⁶ and Bangladesh,²⁷ but consistent to the WHO publication in 2003 that estimated the average adherence to long term therapy for chronic illnesses is 50% in developed countries and even lower in developing countries.²⁸ many other studies have shown variable ratios of good adherence ranging from 40 to 75 %.^{29,30} The different results among different studies

might be due to the different targets of the studies, using different scales to measure the adherence to the drugs, and different sociocultural factors.

About two thirds of our participant had uncontrolled blood pressure; this could be due to stress accompanying visiting a health institution or presence of white coat hypertension. A study in USA which had an approximate result and their participants have adhered to life style modification and treatment though had a higher mean systolic blood pressure has explained this unexpected association by the fact that patient with poorly controlled blood pressure are more motivated to adhere to recommendations.²² Similar to patients with hypertension, two thirds of patients with type 2 DM were uncontrolled. As mortality is significantly increased in patients with poorly controlled HT and T2DM³¹ more care and planning to be done to achieve better control.

About two thirds of the participants considered themselves completely committed to doctor's instructions; this is similar to a study conducted in USA in which 88% of them reported adherence to those recommendations.²² A study in Italy found that 39.3% patients reported themselves as being adherent to medications over the 4 weeks preceding their medical specialist's visit.³²

Many studies have suggested that the non-adherence frequently occurs for a variety of patient-related factors, including socio-demographic and socio-economic characteristics, personal schedules, lack of understanding the diagnosis and treatment, concerns about effectiveness and side effects of treatment, and the desire to manage the situation independent of the medical profession. Possible barriers to adherence include characteristics of the medicines and their dosage and schedules, practical issues related to access to medications, its costs, and physician-patient relationship.³²

In our study, we found a statistically significant association between level of compliance measured by Morisky scale and visit to health institutions other than PHCs. This relationship has been found in a study from Botswana.³³

Pill accounts can be routinely used in clinical practice as it is highly accurate, has a low cost, simple, and can be used for various

drugs formulation.³⁴ We found that drug adherence by this method has a significant statistical association with application of patient life modification.

This study has found that the overall good compliance has a statistically significant association with participants' visiting of health institutions other than PHCs, p value is 0.004. This kind of association might indicate that the drive for good compliance comes from health care providers working in other health institutions than from those working in PHCs and this attitude if it true needs to well-studied and overcome by a comprehensive plan. Many reasons could stand behind this. First, care provided for patients with chronic and non-communicable diseases in the PHCs fall short of the growing needs of patients in recent years and the USAID (PHCPI) in 2011 demonstrated weaknesses in the capacity of the PHC to provide these services.³⁵ Second, is the lack of drugs, supplies and equipment in the local PHC with frequent out of stock of the essential drugs and lab supplies. Although the first line treatment of hypertension and diabetes have been added to the list of essential drugs for PHC, but public clinic act as a source for essential drugs. In addition, adherence to drugs is higher among patients who see the same healthcare provider each time they have a medical appointment. In this group, the average adherence is 81 % as have been stated by "Medication Adherence in America".³⁶ lastly, in Iraq as in most Middle Eastern countries care of NCD is typically provided by specialists who have little involvement with PHCs with a great tendency of the patients to be seen by specialists in secondary and tertiary centres.

This study has also found that the overall good compliance has a statistically significant association with level of communication between the patients and the health care providers, p value is 0.031. The effect of good communication on compliance to drugs is well established.³⁷ However, a study from Al-Madina Al-Monawara in Saudi Arabia has found that a satisfactory communication is reported only in 14.4 % of good drug complaint.³⁸

Limitation of the study: Several limitations of this study deserve to be mentioned. Firstly: limited time prevent us from including more PHCCs and more patients from the enrolled centres. Secondly: due to unavailability of

data, we were unable to include more parameters and to test their link to drug compliance, such as co-morbid chronic diseases, state of control of diseases, and patient's income. Thirdly: unavailability of some laboratory tests like HbA1c at the PHCs prevent us from including this important test in our assessment in the diagnosis and control status of diabetes mellitus.

CONCLUSION

The scales used to detect good drug compliance in patients with Hypertension and/or diabetes mellitus who are visiting PHCs in Iraq are inconsistent. Pill identification test shows the highest rate of good drugs complaints while Morisky scale is the lowest. In general compliance is still poor and by overall compliance scale about two thirds of patients were non-compliant. The level of complaint by overall scale is significantly associated with the patient's attitude to visit health institutions other than PHCs and the effectiveness of patient-health care providers' communication.

REFERENCES

1. The National Strategy for Prevention and Control of Non-Communicable Diseases. Republic of Iraq Ministry of Health, Baghdad. 2013-2017. available at: http://apps.who.int/iris/bitstream/handle/10665/113230/CCS_Iraq_2012_EN_14959.pdf?jsessionid=7E2991F5413761993085961F89B018DA?sequence=1
2. Hashim S, Alsallami A, Abutiheen AA, Hypertensive Patients Compliance with Medications in Marjan Teaching Hospital/ Babylon. *Medical Journal of Babylon* 2015;12(3):592-602. Available: <http://www.medicaljb.com>
3. Hanady M, Abu Hadeed. Prevalence of Depression among Diabetic Patients. Thesis for an-Najah national university/ master degree of community mental health nursing, 2014. [Unpublished study] Available at: <https://repository.najah.edu/bitstream/handle/20.500.11888/6828/Hanady%20Hadeed.pdf?sequence=1&isAllowed=y>
4. Werner ME, Vijver S, Adhiambo M, Egondi T, Oti SO, and Kyobutungi C. Results of a hypertension and diabetes treatment program in the slums of Nairobi: a retrospective cohort study. *BMC Health Services Research* 2015;15:512. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4650397/pdf/12913_2015_Article_1167.pdf
5. Khardori R, Type 2 Diabetes Mellitus Treatment & Management. E-medicine. medscape.com, Accessed on Mar 06, 2018. Available at: <https://emedicine.medscape.com/article/117853-treatment>
6. Khan AR, Al-Abdul Lateef ZN, Al Aithan MA, Bu-Khamseen MA, Al Ibrahim I, Khan SA. *J Family Community Med*. 2012 Jan-Apr;19(1):26–32. Doi: 10.4103/2230-8229.94008. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3326767/>

7. Crowley M, et al. Tailored case management for diabetes and hypertension (TEACH-NIDM) in a community population: Study design and baseline sample characteristics. *Contemp Clin Trials* 2013 September;36(1):1-8. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3828629/pdf/nihms519381.pdf>
8. Conn V S, RN, FAAN, Todd M. Rupp, Maithe Enriquez, Pamela S. Cooper, Patient-Centered Outcomes of Medication Adherence Interventions: Systematic Review and Meta-Analysis. School of Nursing, University of Missouri, Columbia, MO, USA. *Value in health* 2016;19:277-285. Available at: <http://dx.doi.org/10.1016/j.jval.2015.12.001>
9. Gottlieb H, Medication Nonadherence: Finding Solutions to a Costly Medical Problem. 2000 Cliggett Publishing, Division of CMP Healthcare Media, updated Oct 12, 2014. Accessed at 2020-4-20. Available at: <https://www.theweb.ngo/history/ncarticles/Medication%20Nonadherence.htm>
10. Primary Health Care Project. Hypertension Prevention, Diagnosis, and Treatment. Primary Health Care Service Delivery Guidelines. Iraq 2013. Available at: https://extranet.who.int/ncdcs/Data/IRQ_D1_Hypertension-MOH.pdf
11. Primary Health Care Project. Guideline for Diabetes Mellitus and Metabolic Syndrome Management. Iraq April 2012. Available at: <http://www.phd.iq/LionImages/PDFStore/1Diabetes%20and%20Metabolic%20Syndrome-MOH-Revised%20Final%20May%2015%20docs.pdf>
12. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens* 2008;10(5):348-54. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2562622/>
13. Parienti JJ, Verdon R, Bazin C, Bouvet E, Massari V, Larouze B. The pills identification test: a tool to assess adherence to antiretroviral therapy. *JAMA* 2001 Jan 24-31;285(4):412. DOI:10.1001/jama.285.4.412.
14. Steel G, Nwokike J, Joshi M. Development of a Multi-method Tool to Measure ART Adherence in Resource-Constrained Settings: The South Africa Experience. 2007. Available at: https://www.researchgate.net/profile/Jude_Nwokike2/publication/267362525_Development_of_a_Multi-Method_Tool_to_Measure_ART_Adherence_in_Resource-Constrained_Settings_The_South_Africa_Experience_Development_of_a_Multi-Method_Tool_to_Measure_ART_Adherence_in_Resource-Constrained_Settings/links/56ecc44508aed17d09f6784d.pdf
15. American Family Physician. AAFP Core Educational Guidelines. Patient Education. *Am Fam Physician*. 2000 Oct1;62(7):1712-1714. Available at: <https://www.aafp.org/aafp/2000/1001/p1712.html>
16. Albert WD, Batuman V, Epidemiology of hypertension. Medscape/ Updated Dec 29, 2014. Available at: <https://emedicine.medscape.com/article/1928048-overview>
17. Thompson ME & Barth NM. Essential of family medicine book, Nutrition and Weight Management, Chapter 15 page 180. Lippincott Williams & Wilkins, a Wolters Kluwer business, 2012. Available at: http://simidchiev.net/lubokirov/Essentials_of_Family_Medicine_Sloane.pdf
18. Panezai S, Ahmad M and Saqib SE. Factors affecting access to primary health care services in Pakistan: a gender-based analysis. *Development in practice* 2017;27(6):813-827. Available at: <https://doi.org/10.1080/09614524.2017.1344188>
19. STEP wise approach to chronic disease risk factor surveillance, Iraq 2015. Available at: http://www.who.int/ncds/surveillance/steps/Iraq_2015_STEPS_Report.pdf
20. Pineault R, Da Silva RB, Provost S, Fournier M, Prud'homme A, and Levesque JF. Do Gender Predominant Primary Health. *Health Care Organization, Provision, and Financing*, 2017;54:1-9. Available at: <http://journals.sagepub.com/doi/pdf/10.1177/0046958017709688>
21. PHIC- MOH, Palestinian Health Information center, in Ghazza, Palestine/ annular center, 2015. Available at: https://www.site.moh.ps/Content/Books/FDVFRuU5ORaxrOaq4C5Q987a3G-BwllDpumLafURDQJcT7ggdf9Yk13_UEpLZXH64SsaOSyrQeQIE-T7OIJGkpE1QXz48MqlmMZXlgFpARQZQdE.pdf
22. Lenny Lopez E. Francis Cook Mark S. Horng LeRoi S. Hicks, Lifestyle Modification Counseling for Hypertensive Patients: Results From the National Health and Nutrition Examination Survey 1999–2004. *American Journal of Hypertension*, 2009;22(3):325–331. Available at: <https://academic.oup.com/ajh/article/22/3/325/131521>
23. Healthcare Benchmarks 2013: Improving Medication Adherence report. Healthcare intelligence network. Available at: http://www.hin.com/library/2013HealthcareBenchmarksMedicationAdherence_preview.pdf
24. Yassine M, Al-Hajje A, Awada S, Rachidi S, Zein S, Bawab W, BouZeid M, El Hajj M, Salameh P, Evaluation of medication adherence in Lebanese hypertensive patients. *J Epidemiol Glob Health*. 2016;6(3):157-67. Doi: 10.1016/j.jegh.2015.07.002. Epub 2015 Jul 29. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26232704>
25. Sadeq R, Lafta R K, Knowledge, attitude and practice about hypertension in hypertensive patients attending hospitals in Baghdad, Iraq. *South East Asia Journal of Public Health*, 2017;7(1):29-34. Available at: <https://www.banglajol.info/index.php/SEAJPH/article/viewFile/34676/23379>
26. Tibebe A, Mengistu D, Negesa L. Adherence to recommended lifestyle modifications and factors associated for hypertensive patients attending chronic follow-up units of selected public hospitals in Addis Ababa, Ethiopia. *Patient preference and adherence*. 2017;11:323-330. doi:10.2147/PPA.S126382. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338986/>
27. Islam SMS, Biswas T, Bhuiyan FA, Mustafa K, Islam A. Patients' perspective of disease and medication adherence for type 2 diabetes in an urban area in Bangladesh: a qualitative study. *BMC Research Notes*. 2017;10:131. Doi: 10.1186/s13104-017-2454-7. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5361713/pdf/13104_2017_Article_2454.pdf
28. WHO. Adherence to long-term therapies: evidence for action, WHO 2003 report. Available at: http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf
29. Dunbar-Jacob J, Mortimer-Stephens MK, Treatment adherence in chronic disease. *Journal of Clin Epidemiol*. 2001 Dec;54(1):S57-60. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11750211>
30. Shamsi A, Khodaifar F, Arzaghi SM, Sarvghadi F, Ghazi A. Is there any relationship between medication compliance and affective temperaments in patients with type 2 diabetes? *Journal of Diabetes and Metabolic Disorders*. 2014;13:96. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4180133/>
31. Scherthaner G. Cardiovascular mortality and morbidity in type-2 diabetes mellitus. *Diabetes Research and Clinical Practice*, 1996;31:S3-S13. Available at: <https://www.sciencedirect.com/science/article/pii/0168822796012247>
32. Napolitano F, Napolitano P, Angelillo IF. Medication adherence among patients with chronic conditions in Italy. *European Journal of Public Health*, 2016;26(1):48–52. Available at: <https://academic.oup.com/eurpub/article/26/1/48/2467376>
33. Rwegerera GM, Moshomo T, Gollakota S, Mhimbira FA, Fadare J, Godman B, et al. Antidiabetic medication adherence and associated factors among patients in Botswana: implications for the future. *Alexandria Journal of Medicine*, 2018;54: 103–109. Available at: <https://reader.elsevier.com/reader/sd/8F>

A52A13FF64A5C389766A7F5A278F1AA51BB45E7098B56557CA88245D5A7E2D2DE7C687F6ADD7FA4D115759711C9606

34. Lam WY, and Fresco P. Medication Adherence Measures: An Overview. Hindawi Publishing Corporation. *BioMed Research International*. Volume 2015, Article ID 217047,12 pages. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4619779/pdf/BMRI2015-217047.pdf>
35. USAID Primary Health Care Project in Iraq (PHCPI) Baseline assessment report 2011. Available at: <http://www.urc-chs.com/resources/baseline-assessment-report-2011-primary-health-care-project-iraq-usaidphcpi>
36. WHO. Technical package for cardiovascular disease management in primary health care. Access to essential medicines and technology. WHO 2018, WHO/NMH/NVI/18.3. Available at: <http://apps.who.int/iris/bitstream/handle/10665/260420/WHO-NMH-NVI-18.3-eng.pdf;jsessionid=393E68D9D8E1E15599713460EAB9773C?sequence=1>
37. Stephen A. Brunton. Improving Medication Adherence in Chronic Disease Management. *the Journal of Family Practice*, April 2011;60(4):S1-S8. Available at: <https://www.mdedge.com/jfponline/article/76635/health-policy/improving-medi>

cation-adherence-chronic-disease-management

38. Mahmoud MI. Compliance with treatment of patients with hypertension in Al-madinah Al-munawwarah: A community-based study. *Journal of Taibah University Medical Sciences*, 2012;7(2):92-98. Available at: <https://www.sciencedirect.com/science/article/pii/S1658361212000297>



Abbreviations list: Haemoglobin A1c (HbA1c), Hypertension (HT), Milligram per decilitre (mg/dl), Millimetre of mercury (mmHg), Non-communicable diseases (NCD), Pill identification test (PIT), Primary Healthcare Centres (PHCs), Statistical package for social sciences (SPSS), Type 2 diabetes mellitus (T2DM), United states of America (USA), World Health Organization (WHO).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this study a part from self funding.

Fatal injuries among children under five years in southern provinces (Muthana, Thiqr, Basra, and Misan) of Iraq during 2010-2015

Khitam M. Ali,¹ Abdul Sahib H. Abdul Kareem,² F. Lami,³ Ahmed H. Radi,⁴

ABSTRACT

INTRODUCTION: Child injury is a growing but preventable global public health problem. For every person killed by injury, 30 people are hospitalized and 300 are treated in emergency rooms that may live with varying degrees of disability. Every day >2,000 children die from injuries.

OBJECTIVE: Is to describe the epidemiological characteristics, estimate incidence and identify mechanism of fatal injuries among under five years' children (FIU5) in four south provinces (Basra, Misan, Muthana, and Thiqr), Iraq, 2010-2015..

METHODS: This cross-sectional study was conducted on data obtained from Iraqi Injury Surveillance System. The mortality part of the injury surveillance is a population based involving the coroner offices in four south provinces (Muthana, Thiqr, Basra, and Misan), Iraq. U5 population data were obtained from Ministry of Planning.

RESULTS: The total number of reported FIU5 during this period was 1,022 with an average annual incidence of 24.7/100,000 U5 population (U5P). It represents 22.2% of FIU5 and 1.4% of total fatal injuries of all ages. The incidence of FIU5 increased from 17.1/100,000 U5P in 2010 to 28.7/100,000 U5P in 2015. The male to female ratio of FIU5 was 1.6:1 and 28.9% occurred at the age of two years. About 50.1% occurred at home; 79.1% were unintentional and 63% occurred during 6 am-3pm. The main causes of FI were: Road traffic accidents (22.6%), drowning (19.8%), burn (16.9%), electric shock (9.6%), fall (7.3%) and explosions (2.9%). The highest average incidence was reported in Muthana (54.2/100,000 U5P) and Misan (50.3/100,000 U5P) governorates.

CONCLUSION: The increasing incidence of FI is the tip of the iceberg which indicates that every year thousands of U5 are injured and hundreds end with disability. Public Health officials need to develop a comprehensive program to control injuries among young children particularly the traffic and home injuries.

Key words: Fatal, Injury, Epidemiology, Under Five, Iraq.

INTRODUCTION

Injury is a growing global public health problem which can be prevented. As well as being a leading cause of mortality-particularly among children and young adults.¹ Injuries and violence are so common that we often accept them as just part of life. But they can be prevented, and their consequences may be reduced.² The interval from the appearance of injury to death could be immediate, or as long as months or years.³

"Injuries occur when humans are exposed to energy forces that are larger than the body's normal tolerance levels for energy absorp-

tion".⁴ Injury is caused by acute exposure to physical agents such as mechanical energy, heat, electricity; and chemicals. In some cases, for example drowning, injuries result from the sudden lack of essential agents such as oxygen. About three-fourths of all injuries, including most vehicle crashes, falls, and shootings, are caused by mechanical energy.⁵

In the world's high-income countries, for every person killed by injury, 30 people are hospitalized, and 300 are treated in emergency rooms; even more are treated in other health care facilities. This does not reflect the situation in developing countries, which have

¹ MBCHB. Field epidemiologist, Iraqi Cancer Registry Section, Iraqi Cancer Board, Ministry of Health, Baghdad, Iraq.

² Medical Educationist. National Centre for Training and Human Development, Iraqi MoH, Baghdad, Iraq.

³ Professor of Community Medicine. Departments of Community and Family Medicine, College of Medicine Baghdad University.

⁴ Operational Centre and Emergency Medicine, Ministry of Health, Iraq.

Corresponding Author: Khitam M. Ali, Iraqi Cancer Registry Section, Iraqi Cancer Board, Ministry of Health, Baghdad, Iraq.

E mail: dr.Khetam66@gmail.com.

fewer resources for prevention, treatment, and rehabilitation of injuries.⁶

Worldwide, World Health Organization (WHO) estimated that about 16,000 persons die from injuries every day more than 2000 of them are children. Each year one million deaths among under 18 years result from injuries, about 90% of them due to unintentional injuries.⁷

In the Eastern Mediterranean Region (EMR) half a million people die of injuries every year represented 11% of all regional deaths. Injuries in EMR represent the 2nd highest estimated mortality rate in under 5 years (U5) in the world, after the African region.⁸

This study is conducted to estimate the incidence of fatal injuries in south provinces (Muthana, Thiqr, Basra, and Misan) of Iraq among children less than 5 years of age for the period from 2010 to 2015, and to describe some of the epidemiological characteristics like gender, age group, time model, and mechanism of injury.

METHODS

Settings and study design: A descriptive cross-sectional study was conducted to measure death of children under 5 years due to fatal injuries reported to the Coroner Offices (CO) as a part of Iraqi Injury Surveillance System (IISS) in south provinces of Iraq (Muthana, Thiqr, Basra, and Misan) from 2010 to 2015.

Ethical consideration: A written permission for accessing the data was obtained from Operations Centre Department (OCD) at Ministry of Health (MoH). The information of the injured persons is kept secured and protected and has been used only for the sake of this study.

Definition of the participants and exclusion criteria: Data of all children under 5 years who died as a result of an injury in south provinces of Iraq (Muthana, Thiqr, Basra, and Misan) from 2010 to 2015 were included in this study. Data were extracted from IISS. Sexual assaults were excluded from this analysis

Data collection: Data obtained from the records registries of the IISS, OCD at MoH for the period from 2010 to 2015. The IISS is a central registry system established by MoH

in Baghdad in December 2008 as a pilot included only 4 Health Directorates; Baghdad\ Rasafa, Basra, Erbil, and Kerbala. From 2010 to 2012 IISS expanded to involved 8 governorates; Baghdad (Rasafa and Karhk), Basra, Erbil, Kerbala, Misan, Anbar, Mosel, and Sulaimaniya. In 2013, all provinces in Iraq have been involved.

Each Iraqi province has a single CO that records the biodata of the fatalities using a standardized surveillance form; a form that was prepared by MoH in English, Arabic and Kurdish languages with support of experts from the WHO and the Centre for Disease Control and Prevention (CDC). All reports would be transferred to the OCD at MoH in Baghdad on monthly bases by Epi-info software.

Procedure: We took a row data of IISS from OCD\MoH for the period from 2010-2015. The data were examined carefully to remove any duplication. For the sake of our study, data of the fatal injuries affecting children under 5 years were only extracted and subjected for analysis. Children under 5 years populations (U5P) in south provinces (Muthana, Thiqr, Basra, and Misan) in Iraq distributed according to age group from 2010 to 2015 were taken from Ministry of Planning (MoP).⁹ Due to lack of exact figures of 2014, the number of children of under 5 years in south provinces (Muthana, Thiqr, Basra, and Misan) was estimated by calculating the average number of children under 5 years in 2013 and 2015. The number, percentage, trend, and incidence of FIU5 were calculated. From 2010 to 2013 using the data of Basra and Misan only, while from 2014 to 2015 the data of Muthana, Thiqr, Basra, and Misan. The incidence calculated by divided the numbers of injuries over the populations multiply by the constant (100,000).

Statistical analysis: Analysis of data done by using Epi-info and Excel software, and represented in suitable tables and figures.

RESULTS

The total number of fatal injuries under 5 years (FIU5) in south provinces during the period 2010 to 2015 was 1,022. They represented 22.2% of total FIU5 registered in the IISS, see **Table 1**. The average annual incidence of FIU5

Table 1 | Number of injuries and death of all ages and U5 in Iraq and in the southern provinces according to IISS from 2012-2015*

	In Iraq	In south	Percentages to all Iraq
	No (%)	No (%)	
Number of injuries all ages	558 005 (100)	112 208 (100)	20.1
Number of deaths all ages	69 999 (12.5)	12 029 (10.7)	17.1
Injuries under 5	57 664 (10.3)	8 760 (7.8)	15.2
Fatal injuries under 5	4587 (7.9)	1022 (11.7)	22.3

* Registries of the IISS/ MoH has included data for all four provinces in 2014 and 2015, and for only Basra and Misan from 2010 to 2013.

Table 2 | Distribution of FIU5 in Southern Provinces* according to age and gender 2010-2015.

Demographic features		N (%)	Average Annual Incidence
Gender	Male	641 (62.7)	30/100000 †
	Female	380 (37.1)	18.7/100000 ‡
	Unknown (not specified)	1 (0.09)	---
Age group	0 - < 1 year	103 (10.1)	
	1 - < 2 years	235 (23.1)	
	2 - < 3 years	295 (28.9)	
	3 - < 4 years	223 (21.9)	
	4 - < 5 years	166 (16)	
Total		1022 (100%)	24.7/100000 §

* IISS data for all four provinces in 2014 and 2015, and for only Basra and Misan from 2010 to 2013.

† Under 5 years male population

‡ Under 5 years female population

§ Under 5 years population

in southern provinces from 2010-2015 was 24.7/100,000. The trend of incidence is shown in **figure 1**.

The highest number, percentage and average annual incidence of FIU5 was among males 641 (62.7%) with an incidence ratio of 30/100,000 of U5MP, with a male to female

ratio of 1.6:1. The highest number and percentage of FIU5 were among those aged 2 - < 3 years, 295 (28.9%). **See table 2**. The trend incidence was increased among both male and female from 2010 to 2015, **see figure 2**.

The top three causes of FIU5 were traffic accidents 230 (22.6%) followed by drowning 202 (19.8%), then burn 173 (16.9%); with average annual incidence 4.8, 4.1, 3.8/100,000 U5P respectively (**Table 3**). The trend incidence of the top three causes is seen in **figure 3**.

The main place of FIU5 occurs at home 513 (50.1%), on street, high way, or road 253 (24.8%), and in farms and countryside 101 (9.9%) with an average annual incidence of 11.5, 5.7, and 1.9/100,000 U5P respectively, **table 4**. The trend incidence for places of occurrence is seen in **figure 4**.

Regarding the type of intention, the highest number, percentage and the average annual incidence of FIU5 was reported as unintentional injuries 808 (79.1%) with an incidence ratio of 17.5/100,000 U5P, **see table 5**. The trend Incidence is shown in **figure 5**.

The highest distribution of FIU5 was reported in Misan 484 (47.3%) and the lowest in was in Muthana 125 (12.2%), while the highest

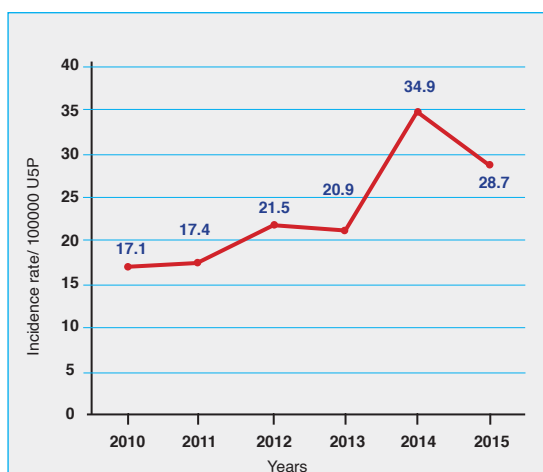


Figure 1 | Trend Incidence of FIU5, in Southern Provinces in Iraq, 2010-2015.

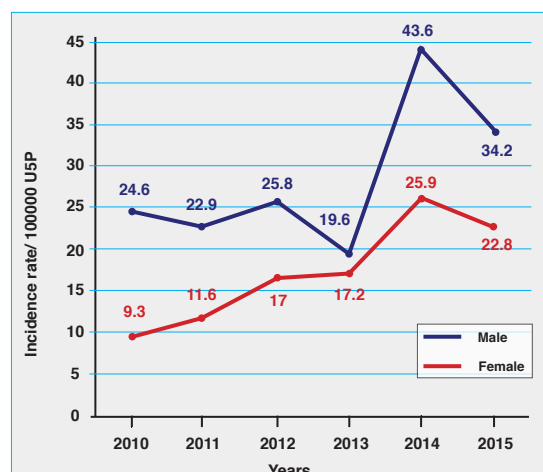


Figure 2 | Trend Incidence of FIU5, in Southern Provinces in Iraq, 2010-2015 according to gender

Table 3 | Mechanisms of FIU5 in southern provinces of Iraq from 2010-2015*, distribution and average annual incidence.

Mechanisms	N (%)	Average Annual Incidence/100000 †
Traffic accidents	230 (22.6)	4.8
Drowning	202 (19.8)	4.1
Burns	173 (16.9)	3.8
Electric injury	99 (9.6)	2.0
Falls	74 (7.3)	1.5
Explosion accidents	30 (2.9)	0.6
Others	214 (20.9)	5.4
Total	1022 (100%)	24.7

* IISS data for all four provinces in 2014 and 2015, and for only Basra and Misan from 2010 to 2013.
† Under 5 years population

average incidence was reported in Muthana 54.2/100,000 of Muthana U5P, and the lowest was reported in Basra 8.7/100,000 of Basra U5P, **table 6**. Regarding the time from injury to arrival to a health facility, the majority was brought within the 24 hours of the injury 688 (67.4%), **figure 6**. However, still 167 victims (16.3 %) were brought after 24 hours from the injury.

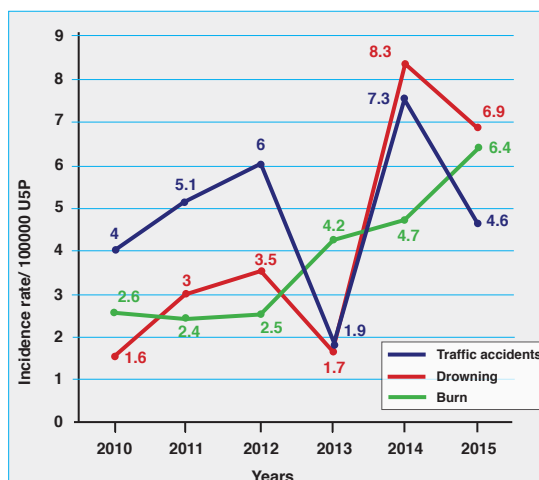
The vast majority of the victims were brought to a health facility using vehicles other than ambulances 931 (91.1 %), while only 85 victims (8.3 %) were brought by ambulances. Four victims (0.4 %) have been brought by other ways and 2 (0.2 %) were not registered.

It is worth mentioning, that only 948 of the registered FIU5 have been specified at which hour of the day the injury had occurred, others are either missed or left blank in the recording system. Most of FIU5 595 (63%) were happened between 6 am to 3 pm, and 353 (37 %) had happened between 4 pm and 5 am.

Table 4 | Place of occurrence of FIU5 in southern provinces from 2010-2015*, distribution and average annual incidence.

Place of occurrence	N (%)	Average Annual Incidence/100000 †
Home	513 (50.1)	11.5
Street/high way/road	253 (24.8)	5.7
Farm and countryside	101 (9.9)	1.9
Public gathering	5 (0.5)	0.1
Workplace	2 (0.2)	0.05
Others/unknown	148 (14.5)	3.4
Total	1022 (100%)	24.7

* IISS data for all four provinces in 2014 and 2015, and for only Basra and Misan from 2010 to 2013.
† Under 5 years population

**Figure 3** | Trend incidence of top three Causes of FIU5, in Southern Provinces of Iraq, 2010-2015.

DISCUSSION

The current study showed an overall increase in the trend incidence of FIU5 from 2010 to 2014; however, a relative decrease in the incidence was noted in 2015. This trend may be the result of unsafe environment that this age group in living in and the lack of comprehensive injury control and prevention programs. In Canada, a study shows that the trends of unintentional injury related deaths for children aged 0-14 from 2003-2012 decreased by 30%.¹⁰

The current study showed that the males experienced higher percentage of injuries in comparison to females, with male to female ratio 1.6:1. The trend curve of incidence of fa-

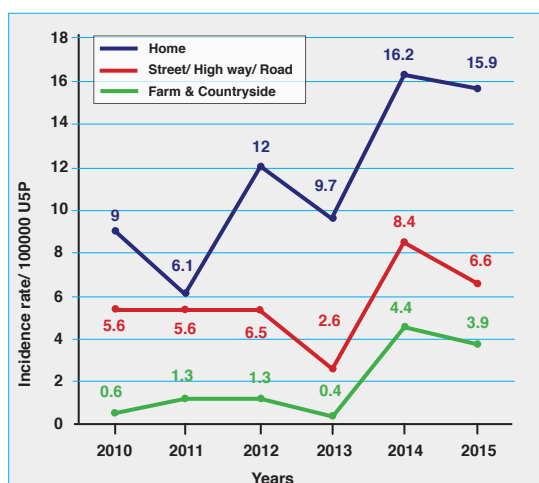
**Figure 3** | Trend incidence of top three places of occurrence of FIU5, in Southern Provinces of Iraq, 2010-2015.

Table 5 | Type of intention of FIU5 in southern provinces from 2010-2015*, distribution and average annual Incidence.

Type of intention	N (%)	Average Annual Incidence\100000 †
Unintentional inflicted	808 (79.1)	17.5
Intentional inflicted	48 (4.6)	1.1
Unknown	166 (16.3)	---
Total	1022 (100%)	24.7

* IISS data for all four provinces in 2014 and 2015, and for only Basra and Misan from 2010 to 2013.

† Under 5 years population

Table 6 | Distribution and average annual incidence of FIU5 in the four southern provinces from 2010-2015*

Provinces	N. (%)	Average Annual Incidence Rate
Misan	484 (47.4%)	50.3/100000 †
Basra	204 (19.9%)	8.7/100000 †
Thiqr	209 (20.4%)	35.9/100000 †
Muthana	125 (12.3%)	54.2/100000 †
Total	1022 (100%)	24.7/100000 †

* IISS data for all four provinces in 2014 and 2015, and for only Basra and Misan from 2010 to 2013.

† Under 5 years population of the relevant province

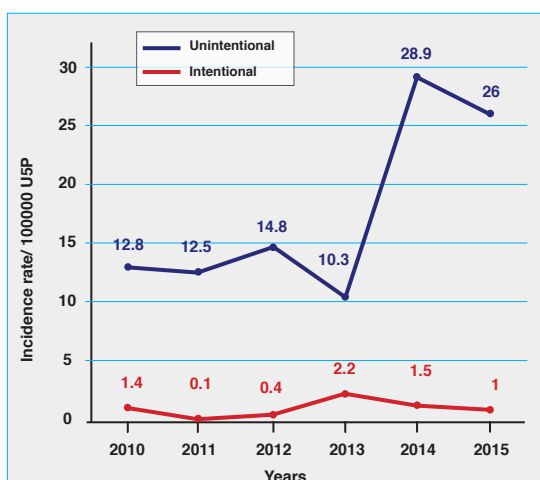


Figure 5 | Trend incidence of FIU5, in Southern Provinces in Iraq, 2010-2015 according to type of intention.

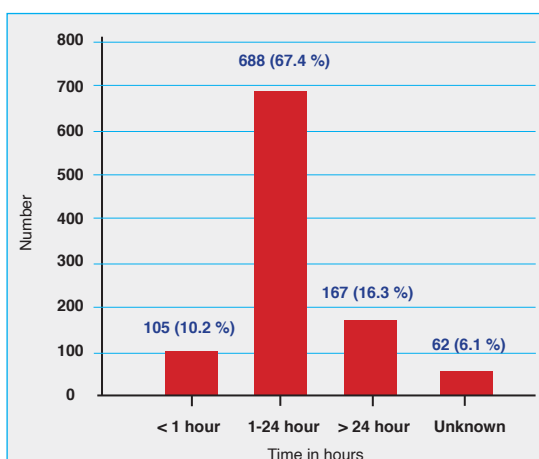


Figure 6 | Time from injury to arrival of FIU5 in Southern Provinces of Iraq, 2010-2015.

tal injuries in both genders showed an overall increase during the studied period with some relative drops, but the drop was more in 2015 for both genders. This gender difference in Iraq may be socio-cultural as girls even during childhood may be more home bounded and less active than boys exposing them to less danger of being victims for injuries. According to the CDC Childhood Injury Report/USA, males had higher injury death rates than females.¹¹ Also, in New Hampshire in USA, a study shows that male children under 5 years who died from injuries between 2005 and 2009 outnumbered females 2.3:1.¹² In Eastern Mediterranean Region (EMR) in 2004, the estimation of FIU5 was nearly doubled in boys than in girls.¹³ In this study, the incidence of FIU5 was increasing in both gender from 2010-2015 in obvious disagreement with the results from Sweden study that showed about 60 % decline in fatal injuries in both genders below age of 20 years over the period from 1987-2001.¹⁴ The difference in the targeted ages may be a cause

for this disagreement.

Our data have shown that children aged 2-3 years are mostly affected by fatal injuries, while those under one year of age are least affected. These results sound logical as former age group is the highly active and energetic while the latter is highly dependent and are always under their parents' close supervision. Two studies from the USA¹⁵ and Scotland¹⁶ have also shown that fatal injuries are more in children less than 1 year comparing to those between 1-4 years.

Regarding the mechanism causing FIU5, the current study showed that the highest number, percentage and incidence, were traffic, drowning, and burn respectively. The incidence of the first three causes of FIU5 has shown that for traffic accidents and drowning the trend curve from 2010-2015 was similarly fluctuated with a relative decline in 2015 after a surge in 2014. While the trend curve for burn has shown a relatively progressive upward

movement. This trend may give us a clue that the family attention about the safety of their children from the injuries occur at home like burn is still low compared to their attention when the children get outside. Rapid urbanization and motorization, lack of appropriate road engineering, and lack of programs of preventing road traffic injury can explain why traffic is the commonest cause of FIU5 in southern Iraq. According to the WHO, over 3,400 people die on the world's roads every day and tens of millions of people are injured or disabled every year. Children, pedestrians, cyclists and older people are among the most vulnerable of road users.¹⁷ In the United States, injuries by motor vehicle are a leading cause of death among children.¹⁸ In 2015, 663 children ages 12 years and younger died as occupants in motor vehicle crashes.¹⁹

In 2004, WHO estimated that 115 boys and 7.4 girls younger than one year/ 100,000, and 9.7 boys and 8.3 girls between 1-4 years/ 100,000 died due to road traffic accidents. In Eastern Mediterranean region the estimation of FIU5 due to road traffic was 18.3/100,000 in high-income countries, and 17.4/100,000 in low and middle-income countries.²⁰ In Germany during the period from 1990-2004, a more than two-thirds decline in fatal injuries of all causes among children under age of 15 years is reported. This decline is true for road traffic, home, and leisure accidents.²¹

For drowning, living near an open source of water as the situation in Iraq prone children for drowning. WHO reported that drowning claimed the life of 360,000 people, ranking it as the 3rd cause of death from unintentional injury. The highest rates of death from drowning are among children 1-4 years, followed by children 5-9 years.²² CDC Childhood Injury Report in the USA has stated that drowning was the leading cause of injury death for those 1 to 4 years of age,¹¹ and it is the second leading cause of unintentional injury death in children aged 1-14 years. Around 4,000 persons died annually from boating and non-boating unintentional drowning, and one in five of them were children 14 years and younger.^{23, 24} Similarly, in 2014 drowning was also a leading cause of FIU3 in Australia, and accounting for 43 % of FIU4 in Bangladesh.²² In Eastern Mediterranean Region in 2004, the estimated mortality of all children's drowning in under 1 year of

age were 4.8 boys and 7 girls/ 100,000, while it was 11.2 boys and 6.8 girls/ 100,000 for those between 1-4 years.¹³

Regarding burn injuries, the highest percentage of burn in our series may be explained by poverty, overcrowding, lack of proper safety measures, and concomitant presence of medical conditions endangering the child for burn like epilepsy. In 2016, WHO estimated that 265,000 deaths every year are caused by burns and child deaths from burns is 7 times higher in low- and middle-income countries than in high-income countries.²⁵ In Colombia from 2000 to 2009, a total of 1,197 fatal paediatric injuries related to burn were identified, about 60 % of them were under 5 years of age and almost half of them died before arriving at a health facility.²⁶ In a systematic review of studies from EMR between 1997 and 2007, burn in under age of 5 years represented 78 % of all childhood burns and 48 % of burn in all ages.²⁷

In our data, the main place of FIU5 occurs at home followed by Street/high way/road then farm and countryside. The trend incidence for all above placed increased progressively from 2010-2015. Usually in Iraq, children spend most of their time at home where they may expose to injuries especially when it comes to drowning and burn. Farms are the houses and workplaces at the same time and due to their relatively larger areas comparing to the usual houses, children are paying little attention and playing unsupervised prone them for injuries. According to the CDC, more than 11,000 individuals are estimated to die each year at home from preventable unintentional injuries.²⁸

According to WHO In 2004, road traffic injuries accounted for approximately 262,000 child deaths among children and youth aged 0-19 years – almost 30% of all injury deaths among children, there are significant geographic variations, however. In the South-East Asia Region, the proportion of childhood deaths due to road traffic injuries is 1.3%, while in the Americas it is as high as 4.7%. Some 93% of child road deaths occur in low-income and middle-income countries. In South-East Asia, however, the rate is 7.4 per 100,000 population. Global road traffic fatality rates increase with age. Children up to the age of nine years are more likely to be accompanied by parents when they travel, either in vehicles or as pe-

destrians, its around rates 9/ 100 000 children Of fatal road-traffic injury for both High-income countries and low-income and middle-income countries , while for those (1-5) years its about 3 child /100000 in high income countries and 9 child /100000 for low-income and middle-income countries.²⁹

About 80 % of FIU5 in our series is unintentional, and its incidence was increasing from 2010-2015. This is expectable as we are living in an environment with many hazards. Injury and violence is a major killer of children throughout the world, responsible for about 950 000 deaths in children and young people under the age of 18 years each year. Unintentional injuries account for almost 90% of these cases. And that road traffic injuries and drowning together account for nearly half of all child death due to unintentional injury.³⁰ In the USA during 2000-2006, each year more than 12,000 people under age of 19 years die from unintentional injuries, mostly caused by burns, drowning, and road traffic, makes them the leading cause of mortality among children in the United States.³⁰

The highest average annual incidence rate of FIU5 was reported in Muthana followed by Misan, Thi qar, and Basra respectively. Is this a real difference between the provinces? Or it is a due to incomplete or inaccurate registration among different provinces, keeping in mind that not all the four provinces were involved in the IISS before 2014. Anyhow other epidemiological and social studies are needed to unfold the real cause.

Regarding the time of arrival to hospitals since injury, although about 80 % of the victims in our series were brought to health facility within the first 24 hours, only about 10 % of the victims were brought within the first hour. Ignorance, misjudgment about the seriousness of the injury, afraid of legal consequences, or lack of a way of transportation or unavailability of a nearby health care facilities could explain this harmful behaviour. This is not inclusive to our country, A study from England done at a trauma centre for injured children showed that only 30 % of injured children under age of 17 years were brought to the centre within 60 minutes of the injury.³¹ It is worth mentioning that the first 60 minutes after injury is usually seen by many trauma experts as the "golden hour" for saving lives.³² and morbidity and mortality

are significantly increased if the time of arriving hospital exceed an hour after an injury.³³ We also found that only less than 10 % of the victims were brought by ambulances, and the vast majority were brought by vehicle other than ambulances. This may occur due to poor knowledge of people about how to contact the ambulances or their believes that ambulances will not come in a short time. In Kampala, Uganda, 2004-2005, a study shows that less than 5% of all injured patients brought to the emergency unit by ambulance.³⁵

Our study ha shown that 63 % of FIU5 was reported between 6 am - 3 pm. This is not strange as we expect injuries to occur usually during working hours. In South India a study done in a tertiary care hospital shows that 52% of the injuries occurred between 8 am and 5 pm.³⁶

This is a retrospective study based on already existed data of Iraqi Injury Surveillance System (IISS). This system has started initially as a pilot to include only some of Iraqi Provinces. This is why we could not include data of all southern provinces for all the studied period.

CONCLUSION

Injuries are still one of the preventable cause claiming the life of the children under age of 5 years in southern provinces especially at age of two years. Most of the fatal death occur at home during the working hours. The causes FIU5 are many but traffic, drowning, and burn are the leading causes. Although most of the victims were brought to a hospital within the first 24 hours after the injury most of them do so by private vehicle other than the ambulances.

REFERENCES

1. World Health Organization. Injuries and violence: the facts 2014. Available at: https://apps.who.int/iris/bitstream/handle/10665/149798/9789241508018_eng.pdf?sequence=1241508018_eng.pdf. Accessed in December 2019
2. The National center for injury prevention and control, CDC. Saving Lives and Protecting People from Injuries and violence. [Online]. Available from: https://www.cdc.gov/injury/pdfs/som_focusarea/NCIPC_FactSheet_O_v14.pdf. [Accessed 6 March 2020].

3. World Health Organization. (2001). Injury surveillance guidelines. Edited by: Holder Y, Peden M, Krug E, Lund J, Gururaj G, Kobusingye O. World Health Organization. Available at: <https://apps.who.int/iris/handle/10665/42451>
4. Krug EG, Sharma GK, & Lozano R. The global burden of injuries. *American journal of public health*, 2000;90(4):523.
5. Baker S, Baker SP, Ginsburg MJ, Li G, O'Neill B. The injury fact book. Oxford University Press, USA; 1992.
6. Krug EG, Mercy JA, Dahlberg LL, Zwi AB. The world report on violence and health. *The lancet* 2002 ;360(9339):1083-8.
7. World health organization. Injuries. Geneva. Available at: <https://www.who.int/topics/injuries/en/>. Access 10 August 2015.
8. World health organization. Violence, injuries and disability Regional meeting of ministry of health focal persons for injury prevention. Emro: 2014. Available at: www.emro.who.int/...injuries.../regional-meeting-of-ministry-of-health-focal-persons.
9. Ministry of Planning. Central Statistical Organization Iraq indicators and figures [internet]. 2012 [access at 10 August 2015]. Available from <http://WWW.cosit.gov.iq/images/publications/iraqnum.pdf> pages (8, 9, 14, 15, and 16)
10. Parachute (2016) Unintentional Injury Trends for Canadian Children, June 2016. Toronto: Parachute. Available at: horizon.parachutecanada.org/wp-content/.../2016/06/SKW-Trend-Report-FINAL.pdf
11. New Hampshire Department of Health and Human Services, Division of Public Health Services. New Hampshire Special Emphasis Report: Infant and Early Childhood Injury, 2005-2009. Available at: <https://www.dhhs.nh.gov/dphs/bchs/mch/documents/child-injury-report.pdf>. Accessed 2016 Aug 16.
12. Sorenson SB. (2011). Gender disparities in injury mortality: consistent, persistent, and larger than you'd think. *American journal of public health* 2011;101(S1): S353-S358.
13. Soori H, Khodakaram S. Child unintentional injury prevention in Eastern Mediterranean Region. *International journal of critical illness and injury science*, 2016;6(1),33. Doi: 10.4103/2229-5151.177366.
14. Ekman R, Svanström L & Långberg B. Temporal trends, gender, and geographic distributions in child and youth injury rates in Sweden. *Injury Prevention*, 2005;11(1),29-32. Doi: 10.1136/ip.2003.005074
15. CDC. Childhood Injury Report: Patterns of unintentional injury among 0 to 19 years old in the United State, 2002-2006. Available at: <https://www.cdc.gov/safekid/images/CDC-childhoodinjury.pdf>
16. Pearson J, and Stone DH. Pattern of injury mortality by age-group in children aged 0-14 years in Scotland, 2002-2006, and its implications for prevention. *BMC pediatrics*, 2009;9(1):26. Available at: <https://bmcpediatr.biomedcentral.com/articles/10.1186/1471-2431-9-26>.
17. World health organization. Violence and Injury Prevention. A 5-year WHO strategy for road traffic injury prevention. Available at: https://www.who.int/violence_injury_prevention/publications/road_traffic/5yearstra/en/.
18. CDC. Web-based Injury Statistics Query and Reporting System [online] National Center for Injury Prevention and Control, Centers for Disease Control and Prevention. Available at: <https://www.cdc.gov/injury/wisqars/fatal.html>. Accessed 10 April 2020.
19. National Center for Statistics and Analysis. (2017, February). Occupant protection in passenger vehicles: 2015 data (Traffic Safety Facts. Washington, DC: National Highway Traffic Safety Administration. Available at: <https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/812374>.
20. World Health organization. Global Burden of Disease: 2004 update. WHO, Switzerland, 2008. Available at: www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf.
21. Ellsäßer G. (2006). Epidemiological Analysis of Injuries among Children under 15 Years of Age in Germany-The Starting Point for Injury Prevention. *Gesundheitswesen (Bundesverband der Ärzte des Öffentlichen Gesundheitsdienstes)* (Germany),2006;68(7):421-428.
22. World Health Organization. Drowning Fact sheet. Updated May 2017. Available at: www.who.int/mediacentre/factsheets/fs347/en.
23. CDC. National Center for Injury Prevention and Control Web-based Injury Statistics Query and Reporting System (WISQARS) [online] [cited 2012 May 3] Available from: <http://www.cdc.gov/injury/wisqars>
24. CDC. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2016. Available at: <http://wonder.cdc.gov>.
25. World Health Organization. Burn Fact sheet. Reviewed September 2016. Available at: www.who.int/mediacentre/factsheets/fs365/en.
26. Aldana MC, and Navarrete N. Epidemiology of a decade of Pediatric fatal burns in Colombia, South America. *Burns*, 2015;41(7):1587-1592.
27. Groohi B, Rossignol AM, Barrero SP, & Alaghehbandan R. Suicidal behavior by burns among adolescents in Kurdistan, Iran: a social tragedy. *Crisis*, 2006;27(1):16-21.
28. Centers for Disease Control and Prevention-Healthy Homes / Healthy Topics / Injury Prevention. Available at: <https://www.cdc.gov/nceh/publications/books/housing/housing.htm>. [Accessed 10 April 2020]
29. Peden M, Oyegbite K, Ozanne-Smith J, Hyder AA, Branche C, Rahman AKMF & Bartolomeos K (2009). World report on child injury prevention (Vol. 2008, pp. 1-28). Geneva: World Health Organization. Available at: https://apps.who.int/iris/bitstream/handle/10665/43851/9789241563574_eng.pdf;jsessionid=CD8FC0E7EEE1D4617B33C74D42228B5B?sequence=1. Accessed 10 April 2020
30. Borse NN, Gilchrist J, Dellinger AM, Rudd RA, Ballesteros MF, Sleet DA. CDC Childhood Injury Report: Patterns of Unintentional Injuries among 0 -19 Year Olds in the United States, 2000-2006. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2008. Available at: <https://www.cdc.gov/safekid/images/CDC-childhoodinjury.pdf>
31. Odetola FO, Mann NC, Hansen KW, Bratton SL. Factors associated with time to arrival at a regional pediatric trauma center. *Prehospital and disaster medicine*. 2016 Feb; 31(1):4-9.
32. Carr BG, Caplan JM, Pryor JP, Branas CC. A meta-analysis of prehospital care times for trauma. *Prehospital Emergency Care*. 2006 Jan 1;10(2):198-206.
33. Rogers FB, Rittenhouse KJ, Gross BW. The golden hour in trauma: dogma or medical folklore?. *Injury*. 2015 Apr 1;46(4):525-7.
34. Newgard CD, Meier EN, Bulger EM, Buick J, Sheehan K, Lin S, Minei JP, Barnes-Mackey RA, Brasel K, ROC Investigators. Revisiting the "golden hour": an evaluation of out-of-hospital time in shock and traumatic brain injury. *Annals of emergency medicine*. 2015 Jul 1;66(1):30-41.
35. Hsia RY, Ozgediz D, Mutto M, Jayaraman S, Kyamanywa P, Kobusingye OC. Epidemiology of injuries presenting to the national hospital in Kampala, Uganda: implications for research and policy. *International journal of emergency medi-*

cine. 2010 Sep ;3(3):165.

36. Abhilash KP, Chakraborty N, Pandian GR, Dhanawade VS, Bhanu TK, Priya K. Profile of trauma patients in the emergency department of a tertiary care hospital in South India. *Journal of family medicine and primary care*. 2016 Jul; 5(3):558.



Abbreviations list: Ante meridiem (am), Centres of disease prevention and control (CDC), Coroner Offices (CO), Eastern Mediterranean Region (EMR), Fatal injuries under age of 3 years (FIU3), Fatal injuries under age of 4 years (FIU4), Fatal injuries under age of 5 years (FIU5), Iraqi Injury Surveillance System (IISS), Ministry of Health (MoH), Ministry of Planning (MoP), Operations Centre Department (OCD), Post meridiem (pm), Under 5 years populations (U5P), Under age of 5 years (U5), United States of America (USA), World Health Organization (WHO).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this study a part from self funding.

Induction outcomes of acute non-burkitt lymphoblastic leukaemia: a data from the Child's Central Teaching Hospital in Baghdad 2011-2015

Sabah Norri Rashid¹, Seemaa Jasim Abd², Vian Alaa Ahmed³, Allawi Noor Hussein Al-Janabi⁴

ABSTRACT

INTRODUCTION: Advances in the study and treatment of paediatric acute lymphoblastic leukaemia are often cited as the paradigm of success in modern clinical trial and translational-research based medicine.

OBJECTIVE: To study the outcomes of induction phase in the treatment of acute lymphoblastic leukaemia in the Haematology-oncology ward of Central Child Teaching Hospital.

METHODS: A retrospective study was conducted on the records of children diagnosed as ALL and received induction phase at the Child's Central Teaching Hospital in Baghdad from 2011-2015.

359 patients below the age of 15 years were included.

RESULTS: Age varied from two months to 14.4 years with a mean age of 5.1 ± 3.2 years. Induction remission in 276 (87.9%), deaths in 35 (11.1%), loss to follow up in 3 (1.0%) patients. Presumptive infection was 1st cause of death in 23 (8.2%) followed by bleeding in 4 (1.3%) of patients.

CONCLUSION: ALL is still a common malignancy in children. Mostly they are of L2 type with standard risk. After induction the majority will pass into remission which is improving in Iraq comparing to the previous published studies. However, mortality is relatively high compared to that in developed countries and infection is the major cause of death.

Key words: Acute lymphoblastic leukemia, Induction mortality, Infection.

INTRODUCTION

Acute leukaemia, the most common form of cancer in children, comprises approximately 30% of all childhood malignancies.¹ Acute lymphoblastic leukaemia (ALL) is the most common malignancy in children. It accounts for one-fourth of all childhood cancers and 72% of all cases of childhood leukaemia.² The peak incidence of ALL occurs between 2 to 5 years of age. The incidence of ALL is higher among boys than girls, and this difference is greatest among pubertal children.³ Due to improvement of treatment of ALL, survival rates have improved dramatically since the 1980s, with a current five-year survival rate of approximately 78%.¹

There are many classifications of ALL based

on morphologic, immunologic, cytogenetic, and molecular genetic characterizations of leukaemic lymphoblast confirming the biologic heterogeneity of this disease.⁴ The widely used morphological classification is the French-American-British (FAB) Cooperative Working Group classification which classifies ALL into L1, L2, and L3.^{5,6} Others are based on Monoclonal antibodies directed against human leukaemia-associated antigens, DNA content by flow cytometry, and genetic translocation. These different classifications aid setting of the diagnosis, treatment and prognosis of ALL.⁷⁻¹¹

The typical symptoms and clinical findings are manifestations of the underlying anaemia, thrombocytopenia, and neutropenia, which in turn reflect the failure of normal haematopoiesis.

¹ MBCHB. FIBMS (ped.), FIBMS (Ped. Haemto/oncology), Child's Central Teaching Hospital, Baghdad, Iraq.

² MBCHB. DOA, anaesthesia, Child's Central Teaching Hospital, Baghdad, Iraq.

³ MBCHB. CABHS-FH, family physician, Baghdad / Iraq.

⁴ MBCHB. DCH, FICMS, CABP, FIBMS (Ped. Haemato/oncology), Child's Central Teaching Hospital Baghdad, Iraq.

Corresponding Author: Allawi Noor Hussein Al-Janabi, Child's Central Teaching Hospital, Al-Karkh Health Directorate, Baghdad, Iraq. E mail: dr_allawinoor@yahoo.com.

sis.¹² Pallor, fatigue, bone pain, petechiae, purpura, bleeding, and fever are commonly present. Lymphadenopathy, hepatomegaly, and splenomegaly are frequent manifestations of extra-medullary leukaemic spread.¹³ In ALL, anaemia exists in approximately 80% of patients on diagnosis. One half of patients has leukocytosis and in 20 % it exceeds 50,000/mm³.¹⁴ Neutropenia of < 500 granulocytes/mm³ is a common phenomenon and is associated with an increased risk of serious infection.¹⁵ Thrombocytopenia occurs in most patients; approximately 75% have < 100,000 platelets/mm³.¹⁶ Definitive diagnosis depends on finding of the specific leukaemic cells in a slide of bone marrow aspirate stained with Romanovsky dye and by the use of special histochemical stains.¹⁷

CNS leukaemia is found at diagnosis of fewer than 5% of children with ALL.¹⁸ With the institution of CNS preventive therapy, routine lumbar puncture (LP) with intra-theal therapy has become an integral part of ALL treatment protocols.¹⁹ Clinically demonstrable testicular disease is rarely present at initial diagnosis; however, occult testicular disease can be diagnosed by biopsy in 25% of newly diagnosed boys.²⁰

TREATMENT: It includes induction, consolidation and maintenance phases. In addition to therapy directed to the CNS. Most of the treatment protocols take two to three years to complete, although the specific regimen varies depending upon immune-phenotype and risk category.²¹

Induction Therapy: The aim of induction is to induce remission which means that the patients have no evidence of leukaemia in the bone marrow and peripheral blood, and absence of detectable CNS or extra-medullary disease.^{22,23} Remission after induction in children with ALL has improved remarkably over recent years with a success rate of 95 %.¹²

Infection is the major cause of treatment-related mortality during the induction phase, so prophylactic antibiotics should be considered in high-risk patient groups and during periods of increased risk.²⁴ After complete remission has been achieved, subsequent therapy is required. Post induction therapy usually consists of consolidation and continuation phases.²⁵

Optimal management of the child with ALL

requires good supportive care including the rational use of blood component therapy, detection and treatment of infections, attention to the metabolic and nutritional needs, and psychosocial support for patient and family.²⁶

In Iraq, years earlier a study was conducted to measure the induction outcome at the Child's Central Teaching Hospital where most of the patients were using pre-phase steroid; a step that has been excluded from treatment protocol thereafter. So, this study is designed to measure the outcomes of induction phase in the treatment of acute lymphoblastic leukaemia in the Hematology-oncology ward of Central Child Teaching Hospital from 2011-2015.

METHODS

Settings and study design: A retrospective descriptive study was conducted at Haematology-Oncology Department at the Child's Central Teaching Hospital during 2016 based on the record of patients with ALL who were admitted during the period between 1st of January 2011 to 31st of December 2015.

Ethical consideration: The protocol of this study was approved by the research committees at the Iraqi Board for medical specialization and at Al-Karkh Health Directorate. Agreement of the hospital administration was also taken to get the data from the records of the patients. Data were kept confidential and only used for the purpose of this study in accordance to the regulations of ministry of Health in Iraq.

Definition of the participants and exclusion criteria: During the studied period, 359 patients below the age of 15 years were included; all were newly diagnosed patients as acute lymphoblastic leukaemia at the Hematology-Oncology unit of the Child's Central Teaching Hospital.

For those patients, data were taken from the medical recording systems (files) that kept in the oncology ward and the medical notebook of each patient that contains all detailed information about inpatients admissions and outpatient's visits. These data included patients' age and gender, residence, duration of onset before referral, date of diagnosis, place

of treatment, and results of biochemical profile, chest X-ray, complete blood count, bone marrow aspiration and cerebrospinal fluid (CSF) examination, and Immune phenotype for some of the patients. Details of induction phase of treatment, progress of the disease during induction, outcome at day 35 from starting chemotherapy, time of death and its presumptive cause were also retrieved.

The final analysis was done on 314 patients after exclusion of 45 patients due to the following reasons: 9 patients with ALL L3 due to their need for different treatment protocol, 5 patients who died before the start of induction therapy, 26 patients because their parents did not accept to start therapy, and 5 patients who have started their treatment outside Iraq and visiting our centre just for follow-up.

In all patients the diagnosis of ALL was established by experienced laboratory haematologists who examined a bone marrow aspirate taken under general anaesthesia. Acute leukaemia was confirmed when the bone marrow slides contained at least 25% lymphoblasts.¹² Morphological classification of the blast cells was done in most patients according to FAB system. Diagnosis of T-cell leukaemia was based on certain clinical and / or laboratory criteria; age >10 years, male gender, mediastinal mass, high initial WBC count, and nuclear cleaving of blast cells by microscopical examination. Immunophenotyping examination were done for some of those patients, while cytogenetic study was not done because it was not available in our centre during the studied period.

According to the treatment protocol received, patients were divided into 2 main groups. **Group I:** those treated with modified MRC UKALL 2003 protocol. **Group II:** treated with Non-Hodgkin's Lymphoma/ Berlin-Frankfort-Munster (NHL/BFM-95) Protocol for T- Cell leukemia. At relevant time, parents or legal guardians are ask to give their written informed consent before starting the treatment.

According to the cell type of acute leukaemia (precursor B or T), we classify patients into risk groups for treatment protocol. **Standard risk (group A)** for patients with precursor B-cell ALL whose age are between 1-9 years and initial WBC count < 50x10⁹/l. **Intermediate risk (group B)** includes patients with precursor B-

cell but their age and initial WBC counts fall outside the range identified in group A. Both A and B groups are treated by MRC UKALL 2003 protocol.²⁷ while **high risk (group C)** includes patients with clinical and morphological suspicion or proved immunophenotypically as T- cell ALL and treated by NHL/BFM-95 protocol.²⁸

After starting induction with MRC-UKALL 2003 protocol, we assess BM response at day 28 or 35 by routine light microscope and categorize the response as:²³ M1 marrow < 5% blasts, M2 marrow 5-25% blasts, and M3 marrow >25% blasts. CNS involvement was diagnosed by the consensus criteria as follows:⁵⁸ CNS-1: where no evidence of leukaemic lymphoblasts in the CSF. CNS-2: < 5 WBCs/ μ l with definable blasts on cytocentrifuge examination, or traumatic LP.²⁹ CNS-3: $\geq$ 5 WBCs/ μ l with blast cells or cranial nerve palsy.

Outcome of Induction: The outcome of induction is assessed at day 28 or 35 from the start of treatment.³⁰ The outcome could be:

Complete remission (CR): Patient's peripheral blood values must be within the normal range, and the bone marrow must be of normal cellularity, with fewer than 5% lymphoblasts.²³ Those who failed to attain CR after 35 days of induction therapy were regarded as no remission. If BM is diluted at day 28 but fulfilling the criteria of remission at day 35 or 42, it is considered as remission.

Induction death: Induction death was defined as death within 35 days from starting chemotherapy.²³

Loss of follow up: It is considered when the family decided to stop treatment and get their child out of the hospital on their responsibility. All patients were received supportive therapy like blood and/or their products, antibiotics, and antifungal treatment according to clinical condition.

Statistical analysis: Statistical package for social sciences version 20 (SPSS 20) was used for data analysis. Kaplan Meier cohort analysis was used to test the significance of studied factor upon survival.

RESULTS

This study enrolled 314 patients as Acute

Table 1 Demographic distribution of study sample		
Variable	N = 314	%
Sex		
Male	175	55.7
Female	139	44.3
Age Group		
< 1 year	10	3.2
1-9 years	265	84.4
10-14 years	39	12.4
Year of Diagnosis		
2011	38	12.1
2012	50	15.9
2013	96	30.6
2014	67	21.3
2015	63	20.1
Province		
Baghdad	114	36.3
Other provinces	200	63.7

non-burkitt Lymphoblastic Leukaemia patients who received treatment during 2011-2015. The annual rate of new cases diagnosed and treated in our centre is 62.8 case/ a year. Age varied from two months to 14.4 years with a mean age of 5.1 ± 3.2 years. Males are commonly affected than females 175 (55.7), for other demographic features see **table 1**.

Table 2 shows the presenting features of the sample. Of them, 201 patients (64.0%) were of standard risk and 92 (29.3 %) were of intermediate risk. Pallor was the commonest presenting symptoms 302 (96.2 %) and splenomegaly is the commonest signs reported in 225 patients (71.9 %).

Table 3 shows the haematologic, serum uric acid and CNS status of the sample.

After induction of therapy 276 (87.9 %) achieved remission, and 35 patients (11.1 %) died. In 23 patients (65.7 %), infections were the cause of death, **see table 4**. **Figure 1** shows the Kaplan Meier curve of survival.

DISCUSSION

Acute lymphoblastic leukaemia is the most common childhood cancer. It constitutes approximately 25% of cancers in children. We found that the children between 1-9 years were mostly affected; 265 patients (84.4 %),

Table 2 Clinical characteristics of studied sample		
Variable	N=314	%
Duration of Symptoms		
< 6 weeks	257	81.8
6 weeks - 6 months	55	17.5
> 6 months	2	0.6
Subtype		
L1	138	43.9
L2	147	46.8
T-cell leukaemia	21	6.7
Undifferentiated	8	2.5
Treatment Protocol		
Standard Risk *	201	64.0
Intermediate Risk **	92	29.3
T-cell ALL protocol	21	6.7
Clinical Features		
Pallor	302	96.2
Fever	287	91.4
Splenomegaly	225	71.9
Hepatomegaly	206	65.8
Bleeding	115	36.6
Lymphadenopathy	108	34.5
Mediastinal Mass	25	8.0

* One patient out of 201 (0.5%) did not respond to standard Risk Protocol and then changed to High Risk Protocol at day 15.

** Two patients out of 92 (2.2%) did not respond to Intermediate Risk Protocol and then changed to High Risk Protocol at day 8.

while those below age of one year was the least affected; 10 patients (3.2 %). This was nearly compatible to the results of Abdullah³¹ in his study conducted in our centre on children diagnosed with ALL from 2009-2011 and Ghali³² in a study conducted at Children Welfare Teaching Hospital Al-Rasafa in Baghdad from 2000 to 2009. Also, it is nearly similar to the results of many other studies from China,³³ India,³⁴ and Jordan.³⁵

Male to female ratio in our study was 1.25: 1. A result which is similar to that from other national and nearby countries; Abdullah find it 1.34:1,³¹ Ghali HH 1.2:1,³² and Halalsheh in Jordan 1.3:1.³⁵ Studies from China³³ and India³⁴ though have shown a male predominance but their ratios were relatively higher; 1.63:1 and 2.1:1 respectively. This may be attributed to some genetic or environmental causes.

We reported that the number of ALL diagnosed and started treatment have increased progressively. the highest number was diagnosed in 2013, 96 patients (30.6%), which is nearly double compared to the result in the

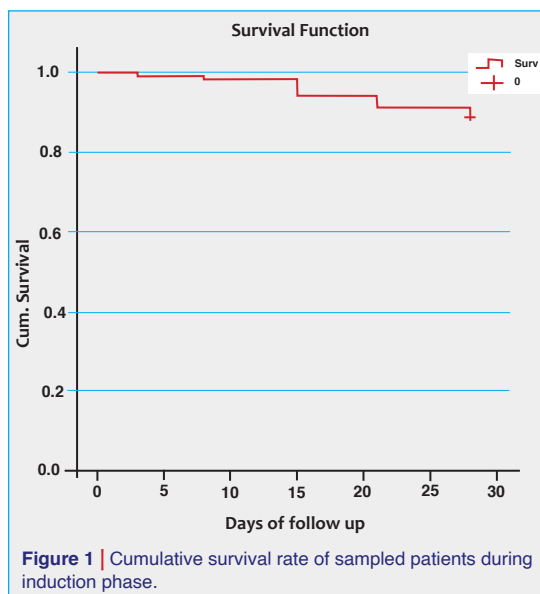
Table 3 | Laboratory findings of studied sample

Variable	N=314	%
Initial Hb level		
< 6 g/dl	68	21.7
6-10 g/dl	209	66.5
> 10 g/dl	37	11.8
Not Recorded	1	0.3
Initial WBC Level (10⁹/L)		
< 10	126	40.3
10-49	122	39.0
≥ 50	65	20.8
Platelets (10⁹/L)		
< 20	86	27.4
20-100	178	56.7
> 100	50	15.9
Serum uric acid level		
Normal (< 420 μmol/l)	276	87.9
Elevated (≥ 420 μmol/l)	34	10.8
Not Recorded	4	1.3
Initial CSF cells		
CNS1	294	93.6
CNS2	13	4.1
CNS3	4	1.3
Not Recorded	3	1.0

2012, 50 (15.9 %). This was because in 2013 the Children Welfare Teaching Hospital, the hospital which has the catchment area from Al-Rasafa in Baghdad, has been closed for reconstruction leaving our centre as the only centre in Baghdad to receive children with haematologic malignancies. Baghdad was the most frequent province of residence of patients in our study 114 (36.3%), other patients were mostly from the nearby provinces like Babil, Anbar, Najaf, Diwania, Karbala, and Muthana

Table 4 | Induction outcome and causes of mortality during induction phase

Variable	N=314	%
Induction Outcome		
Remission	276	87.9
Loss to follow up	3	1.0
Died	35	11.1
Cause of Death		
Infection	23	65.7
Infection & bleeding	4	11.4
Bleeding	4	11.4
Tumour lysis syndrome	2	5.7
Thrombo-embolic Stroke	2	5.7
Alive	279	88.9

**Figure 1** | Cumulative survival rate of sampled patients during induction phase.

which they did not have pediatric haematology centers at the time of the study.

Most of the patients, 257 (81.8%), in our series had their symptoms for less than 6 weeks before diagnosis and it was very rare to see a delay for more than 6 months, only in 2 patients (0.6 %). This is similar to the data reported by Abdullah³¹ and Ghali.³² The acuteness of alarming symptoms of ALL, in addition to the rapid response of the family and the primary care physicians and the availability of basic investigations could explain this result.

The commonest symptoms at presentation were pallor 302 (96.2), followed by fever 287 (91.4%) comparable to those reported by Abdullah³¹ (pallor 96.2%, fever 86.6%). We reported that splenomegaly was the commonest sign elicited in those patients 225 (71.9%) followed by hepatomegaly seen in 206 patients (65.8 %). Abdullah³¹ nearly reported similar figures. However, Ghali³² has reported less fever and more common hepatomegaly than splenomegaly in his study. Advani from India agrees with Ghali's result regarding hepatomegaly.³³

Regarding the laboratory investigations, on presentation most of the patients, 277 (88.2%), were having a hemoglobin level of less than 10 g/dl. And in 209 patients (66.5%) the hemoglobin level was between 6-10 g/dl. Nearly same percentage was reported by Abdullah.³¹ Ghali has reported anemia in only 51.5%.³²

WBC count over 50 x10⁹/l is a marker of a high-risk group of patients. In 248 patients

(79 %), the initial WBC count was less than $50 \times 10^9/L$, and only 65 patients (20.3 %) have their count over $50 \times 10^9/L$. Most other national and international studies were reported a higher rate of WBC count of more than $50 \times 10^9/L$; in Iraq, it ranged between 24.6 %³¹ and 26.4 %, ³² while it was less than a third of patients in the report of the Berlin-Frankfurt-Munster group³⁶ and 28.8 % in a study from Pakistan.³⁷

In our study, primary CNS involvement (CNS-3) was seen only in 4 patients (1.3%) which is slightly less comparing with previous Iraqi studies where it was 2.5 % ³¹ and 3.6%,³² and with a study from western countries where it was 2.4 %.³⁶ We found that CNS-2 grade in 13 patients (4.1%) which is also lower than that reported by Abdullah 7.1%,³¹ and Fadoo 5.8%.³⁷

The commonest subtype of ALL in our series was L2 reported in 147 patients (46.8 %). Abdulla and Ghali have also reported that L2 is the commonest ALL subtype though of more percentages 68.6 and 73.8 % respectively.^{31, 32}

The outcome of induction phase reveals that we achieved remission in 276 patients (87.9%), while unfortunately death was reported in 35 patients (11.1%), and we lost follow up of 3 patients (1.0%) which is far away from the Western studies like Schrappe et al,³⁶ in a study conducted in three European countries Germany, Austria, and Switzerland, has reported a much better outcome than ours where remission achieved in more than 97 % with only 1 % death and another 1% abandonment.

This study showed a better outcome of induction phase but higher mortality rate than that of Abdullah conducted in our centre years ago;³¹ 85% achieved complete remission, 5.7% death and 6.4% loss to follow up. the higher rate of loss of followup in Abdullah's study might be the cause for lower mortality despite higher remission rate. Ghali's has reported 15.6 % mortality rate in his study,³² which is higher than ours.

The commonest presumptive cause of death was infection 23 (65.7 %) followed by bleeding in 4 patients (11.4 %) and other 4 patients (11.4 %) died because of infection and bleeding.

Compared to Schrappe et al,³⁶ who claims

achieving remission in 97 %, we are still behind. Attention for applying infection control policies, raising the infrastructures of the hospital to improve hygiene, proper use of antibiotics, and good education of families about the seriousness of infections and how to protect the child during induction phase from them are very important factors that we should work on in order to improve our rate of remission and to save our children this dreadful fate.

CONCLUSION

ALL is still a common malignancy in children. Mostly they are of L2 type with standard risk. The commonest presentation were anaemia and fever. More than two thirds of the patients have hepatosplenomegaly. CNS involvement is not common. After induction the majority will pass into remission which is improving in Iraq comparing to the previous published studies. However, mortality is relatively high compared to that in developed countries and infection is the major cause of death.

REFERENCES

1. SEER Cancer Statistic Review, 1973-1999. National Cancer Institute, Bethesda MD, 2000; p.467.
2. Stanulla M, Schrappe M. Treatment of childhood acute lymphoblastic leukemia. *Semin Hematol* 2009;46(1):52-63.
3. Stat bite: estimated new leukemia cases in 2008. *J Natl Cancer Inst* 2008;100(8):531.
4. Bernt K, Armstrong S. Leukemia stem cells and human acute lymphoblastic leukemia. *Semin Hematol* 2009;46(1):33-8.
5. Behm F. Classification of acute leukemias: perspective 2. In: Treatment of acute leukemias: new directions for clinical research. Totowa, NJ: Humana Press, 2003:43.
6. Bennett JM, Catovsky D, Daniel MT. Proposals for the classification of the acute leukemias. French-American-British (FAB) co-operative group. *Br J Haematol* 1976; 33:451.
7. Miller DR, Leikin S, Albo V. Prognostic importance of morphology (FAB classification) in childhood acute lymphoblastic leukaemia (ALL). *Br J Haematol* 1981; 48:199.
8. Melnick SJ. Acute lymphoblastic leukemia. *Clin Lab Med* 1999;19:169-86.
9. Trueworth R, Shuster J, Look T. Ploidy of lymphoblasts is the strongest predictor of treatment outcome in B-progenitor cell acute lymphoblastic leukemia of childhood: a Pediatric Oncology Group study. *J Clin Oncol* 1992; 10:606-13.
10. Heerema NA, Sather HN, Sensel MG. Prognostic impact of trisomies of chromosomes 10, 17, and 5 among children with acute lymphoblastic leukemia and high hyperdiploidy (50 chromosomes). *J Clin Oncol* 2000; 18:1876-87.
11. Raimondi SC, Peiper SC, Kitchingman GR. Childhood acute

- lymphoblastic leukemia with chromosomal breakpoints at 11q23. *Blood* 1989; 73:1627–34.
12. Judith FM, Karen RR, Steuber CP. Acute Lymphoblastic Leukemia. In: Principles and Practice of Pediatric Oncology (6th ed), Pizzo PA, Poplack DG (Eds), Lippincott-Raven, Philadelphia, 2011. p.518.
 13. Mastrangelo R, Malandrino R, Riccardi R. Clinical implications of glucocorticoid receptor studies in childhood acute lymphoblastic leukemia. *Blood* 1980; 56:1036–40.
 14. Chang CY, Chiou TJ, Hsieh YL. Leukemic infiltration of the urinary bladder pre-senting as uncontrollable gross hematuria in a child with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol* 2003;25:735–9.
 15. Kadan-Lottick NS, Ness KK, Bhatia S. Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. *JAMA* 2003; 290:2008–14.
 16. Bodey GP, Buckley M, Sathe YS. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med* 1966; 64: 328–40.
 17. Armata J, Grzeskowiak-Melanowska J, Balwier W. Prognosis in acute lymphoblastic leukemia (ALL) in children preceded by an aplastic phase. *Leuk Lymphoma* 1994; 13:517–8.
 18. Bunin NJ, Pui CH, Hustu HO. Unusual extramedullary relapses in children with acute lymphoblastic leukemia. *J Pediatr* 1986; 109:665–8.
 19. Bleyer WA. Central nervous system leukemia. *Pediatr Clin North Am* 1988; 35:789–814.
 20. Bleyer WA. Biology and pathogenesis of CNS leukemia. *Am J Pediatr Hematol Oncol* 1989; 11:57–63.
 21. Steinbach D, Wittig S, Cario G. The multidrug resistance-associated protein 3 (MRP3) is associated with a poor outcome in childhood ALL and may account for the worse prognosis in male patients and T-cell immunophenotype. *Blood* 2003; 102:4493.
 22. Rubnitz JE, Lensing S, Zhou Y. Death during induction therapy and first remission of acute leukemia in childhood: the St. Jude experience. *Cancer* 2004; 101:1677.
 23. Pui CH, Campana D. New definition of remission in childhood acute lymphoblastic leukemia. *Leukemia* 2000; 14:783–5.
 24. Pui CH, Campana D, Pei D. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med* 2009; 360:2730–41.
 25. Harris MB, Shuster JJ, Pullen DJ. Consolidation therapy with anti-metabolite based therapy in standard risk acute lymphocytic leukemia of childhood: a Pediatric Oncology Group Study. *J Clin Oncol* 1998; 16:2840–7.
 26. David. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003: *Blood*. 2014; 124(7):1056–61.
 27. Hann I, Vora A, Richards S. Benefit of intensified treatment for all children with acute lymphoblastic leukaemia: results from MRC UKALL XI and MRC ALL97 randomized trials. UK Medical Research Council's Working Party on Childhood Leukaemia. *Leukemia*. 2000; 14:356–63.
 28. Reiter A, Schrappe M, Parwaresch R. Non-Hodgkin's lymphomas of childhood and adolescence: result of a treatment stratified for biologic subtypes and stage – a report of the Berlin-Frankfurt-Munster group. *Journal of clinical Oncology* Feb 1, 1995:359–72.
 29. Howard SC, Gajjar AJ, Cheng C. Risk factors for traumatic and bloody lumbar puncture in children with acute lymphoblastic leukemia. *JAMA* 2002; 288:2001–2007.
 30. Steinherz PG, Gaynon PS, Breneman JC. Cyto-reduction and prognosis in acute lymphoblastic leukemia; the importance of early marrow response: report from the Children Cancer Group. *J Clin Oncol* 1996; 14:389–98.
 31. Abdullah EA. Outcome of induction phase of Acute Lymphoblastic Leukemia at Central Child Teaching hospital, Baghdad. *Iraqi Medical J*, June 2013; 59(1):1–8.
 32. Ghali HH. Effectiveness of Modified UKALL protocols in Children with Acute Lymphoblastic Leukemia; an experience of Children Welfare Teaching Hospital; *Mustansiriyah Medical Journal*, December 2014;13(2):53–60.
 33. GU L J , LI J , XUE H L. Clinical outcome of children with newly diagnosed acute lymphoblastic leukemia treated in a single center in Shanghai, China. *Leukemia & Lymphoma*, March 2008;49(3):488.
 34. Advani S, Pai S, Venzon D. Acute lymphoblastic leukemia in India: An analysis of prognostic factors using a single treatment regimen. *Annals of Oncology*, 1999; 10: 167–76.
 35. Halalsheh H, Abuirmeileh N, Rihani R. Outcome of childhood acute lymphoblastic leukemia in Jordan. *Pediatr Blood Cancer*. 2011 Sep; 57(3):385–91.
 36. Schrappe M, Reiter A, Zimmermann M. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM Study Group from 1981 to 1995. *Leukemia*. 2000; 14:2205–22.
 37. Fadoo Z. Clinical Features and Induction Outcome of Childhood Acute Lymphoblastic Leukemia in a Lower/Middle Income Population: A Multi-Institutional Report from Pakistan. *Pediatr Blood Cancer* 2015; 62:1700–8.



Abbreviations list: Acute lymphoblastic leukaemia (ALL), Bone marrow (BM), Central Nervous system (CNS), Cerebrospinal fluid (CSF), Complete remission (CR), Cubic millimetre (mm³), Deoxyribonucleic acid (DNA), French-American-British (FAB), Lumbar puncture (LP), Medical Research Council United Kingdom Acute lymphoblastic leukaemia (MRC UKALL), Microliter (μl), Non-Hodgkin's Lymphoma/ Berlin-Frankfurt-Munster group (NHL/BFM), Number (N), Statistical package for social sciences (SPSS), White blood cell (WBC).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this study a part from self funding.

Is it possible to encounter a patient with primary splenic tuberculosis during your career?

Mohammad Yahya Abdulrazaq¹

ABSTRACT

Splenic tuberculosis is an extremely rare variant of extrapulmonary tuberculosis especially in immune competent person. It is usually presented as nonspecific symptoms leading to delay in the diagnosis. Here, we are reporting a 28 year-old female from Baghdad, who was presented with splenomegaly, fever and sweating of 4 months duration. After having a nonspecific laboratory investigation and poor response to broad spectrum antibiotics, splenectomy was done for her, and histopathological examination showed granulomas with caseation. The patient is diagnosed as primary splenic tuberculosis and was registered in the National Specialized Centre for Chest and Respiratory Disease.

Antitubercular medication was prescribed for her after splenectomy for a complete course of 6 months duration with a full improvement in the general condition of the patient. Tuberculosis is still a possible cause of splenomegaly and the patient should be treated with full course of anti TB medication even after splenectomy.

Key words: tuberculosis, spleen, caseated granulomas.

INTRODUCTION

In 2017, tuberculosis (TB) caused an estimated 1.6 million deaths, making it the leading cause of death from a single infectious agent worldwide and the tenth cause of death overall.¹

This disease presents with diverse clinical symptoms, including both pulmonary TB and extrapulmonary TB. Extrapulmonary TB accounts for almost 15% of all cases. Among the extrapulmonary forms, majority are seen in lymph nodes, pleura, genito-urinary tract, bones, meninges, gastro-intestinal tract, peritoneum, and pericardium. Splenic TB is unusual. This form of TB is normally seen as part of miliary TB.² Isolated splenic tuberculosis is extremely rare, particularly in the immunocompetent patient.³

Even if tuberculosis is a familiar condition, an unusual presentation may disguise its correct nature, expressing itself as cases of unexplained fever and splenomegaly in TB en-

demic areas.⁴ So, tuberculosis of spleen must be kept in mind while evaluating fever of unknown origin in any patient on immunosuppressant treatment or having HIV and even in immunocompetent patients as well. Treatment with antitubercular medication is rarely unsuccessful.⁵

Splenic TB is likely to be misdiagnosed as carcinoma of spleen, splenic abscess, lymphoma, or others. The misdiagnosis rate is high if there is no tuberculosis history in other organs.⁶

There are also some reports of spontaneous splenic abscess, causing acute abdominal pain and clinical hypersplenism with bleeding tendencies.⁷

At present there are few cases of solitary splenic tuberculosis reported in the literature internationally, and through the literature retrieval, there are no reports about splenic tuberculosis mortality rate data.⁸

CASE PRESENTATION

A 28-year-old female from Baghdad was referred to the National Specialized Centre for Chest and Respiratory Disease to have an opinion regarding accidental histopathologic finding of caseating granulomas in a tissue specimen of spleen post splenectomy.

The history of the patient was dated back to 4 months before the splenectomy where the patient started to complain of pain in the left hypochondrial region and vague diffuse abdominal discomfort. Progressively patients developed low grade fever and sweating with vague ill health. Patient had no history of cough or significant weight loss. Initial medical consultation and simple laboratory investigation were not yielding to a diagnosis and treatment with antibiotic and analgesia failed to show any response.

Patient reported no significant medical, surgical and drug history. And her gynaecological history was unremarkable. She was not smoker has no history of contact with a patient known to have pulmonary tuberculosis or any other infectious diseases.

On clinical examination the patient was ill looking, with high temperature (37.8 °C), mild tachycardia with normal blood pressure. Cervical and axillary lymph nodes were not palpable. She was neither pale nor icteric. Chest examination was essentially normal while abdomen was distended with tender palpable spleen below the left costal margin and signs suggested of ascites.

Complete blood count was within normal limit. GPT, GOT, and alkaline phosphatase were mildly elevated, while renal function test, general urine examination, total serum bilirubin and serum albumin were within normal. Chest X ray showed no abnormality while abdominal ultrasound showed moderate splenomegaly with moderate ascites. Electrocardiography and echocardiography were within normal. The treating physician was thinking to exclude tumour like lymphoma or ovarian or other gastrointestinal malignancy. So, decision was made to do bone marrow aspiration which showed no significant pathology. Aspiration of peritoneal fluid which was exudative revealed cellular smear with moderate count of lymphocyte predominant mixed inflammatory cells

and few hyperactive macrophages with no RBCs or atypical cell. Bacteriological examination of the peritoneal fluid was not yielding and unfortunately, Genxpert was not used to verified the diagnosis of Mycobacterium tuberculosis infection because TB was not suspected at this early stage.

Absent of response to treatment and non-specific investigation turned to decision to do splenectomy which was done under general anaesthesia. The gross pathological finding showed a spleen of 23x17x6 cm, brown in colour, and soft to firm consistency. Serial microscopic section showed splenic tissue with reactive lymphoid changes of white pulp and patchy replacement of red pulp by numerous small size non-caseating and minimally caseating active granulomas with Langerhans giant cells and secondary splenic fibrosis. With a suspicion of primary tuberculosis of the spleen.

At our centre, searching for latent or active pulmonary Tuberculosis were negative. Based on histopathological findings, poor response to preliminary antibiotics and absence of confirming diagnosis of malignancy the patient was diagnosed as a primary splenic TB and registered as an extra pulmonary TB case in the national TB program in Iraq. Antitubercular medication was prescribed for a complete course of 6 months duration started as 2 months initial phase with 4 tablets of combined fixed dose 4 drugs formula; Isoniazid 75 mg, Rifampicin 150 mg, Pyrazinamide 400 mg, and ethambutol 275 mg. Then followed by 4 months continuation phase with 4 tablets of combined fixed dose 2 drugs formula; Isoniazid 75 mg and Rifampicin 150 mg. Monitoring of the patient during the treatment course was uneventful. Progressively, the patient became clinical well without fever. Abdominal pain subsided and appetite has improved remarkably. Abdominal ultrasound post treatment was normal.

DISCUSSION

Tuberculosis continues to be a major health problem worldwide, despite considerable advances in the diagnosis and treatment of the disease.⁹

Abdominal TB which contributes to a mere 3% of all extrapulmonary TB encompasses

gastrointestinal tract, peritoneum, omentum, mesentery, regional lymph nodes and solid organs like liver, spleen and pancreas.¹⁰ Isolated abdominal solid organ TB is rare in immunocompetent individuals. The incidence of splenic TB is 0.14-0.7% as per autopsy-based studies.^{2,11} A non-systematic review to search for published cases of splenic tuberculosis in immunocompetent patients between 2000 and 2019 found only 31 cases with tuberculous involvement of spleen.¹²

Although Iraq is endemic with tuberculosis, primary splenic tuberculosis is also extremely rare, and here we are reporting this case of isolated tuberculosis of the spleen which was presented with splenomegaly and ascites and it is the first reported case to the National Specialized Centre for Chest and Respiratory Diseases up to our knowledge.

Splenic TB occurs in two forms. The first form is part of miliary TB, which occurs especially in immunocompromised patients.¹³ The second, and the unusual form is primary splenic TB where spleen is the primary site of involvement, as in our patient.² Splenic tuberculosis usually occurs secondary to haematogenous spread of a primary infection, as a part of disseminated disease.¹⁴ morphologically, splenic tuberculosis occurs in five types miliary, nodular, spleen abscess, calcific and mixed type.²

Patients susceptible to acquiring splenic tuberculosis usually have one of the following risk factors: immunosuppression, preceding pyogenic infections, splenic abnormalities, prior trauma to the spleen, sickle cell disease and other haemopathies, and in the immunocompetent patient another body site infected by *M. tuberculosis*.³ Study done by Dixit et al over a period of 3 years in an Indian hospital found only 16 patients (0.01%) with splenic involvement from a total of 9205 TB patients and were able to identify a cause for immunodeficiency in only 9 of those 16 patients (8 with HIV infection and 1 with myelodysplastic syndrome). Ten of those 16 patients in their study had pulmonary involvement too.¹⁵

In our report, we present a young immunocompetent female with primary splenic tuberculosis. Extensive history, comprehensive clinical examination and basic laboratory investigations failed to find any disease or con-

dition that jeopardize her immune status. In addition, her lungs were free of tuberculous process.

Clinical manifestations are non-specific like anorexia, fever, malaise, weight loss, night sweats, abdominal pain and jaundice. Splenic TB can present as splenomegaly, hypersplenism, solitary splenic lesion or splenic abscess.^{16,17,18} Rarely, patients can be asymptomatic and their diagnosis is delayed.³ Other severe presentations include splenic rupture, portal hypertension with and without gastrointestinal bleed, and fulminant form involving rapid progression of fever, cachexia, haemorrhage and sepsis. Patients with splenic tuberculosis can also present with haematologic abnormalities: usually they are cytopenic due to hypersplenism, but cases of polycythemia have also been reported.^{19,18,20} Our case was presented with nonspecific symptoms, pyrexia of unknown origin was the prominent presentation. Other constitutional symptoms were mild to moderate and this might be the cause of delay in the diagnosis. Also, clinical examination was normal except for splenomegaly and ascites.

Diagnosis of isolated splenic tuberculosis is difficult and often delayed because of vague clinical manifestations. In almost all the reported cases diagnosis was suggested by radiologic examination and confirmed by pathologic examination of fine needle aspiration, splenic biopsy or of splenectomy specimen. Some times the diagnosis was made by direct detection of the mycobacterium tuberculosis bacilli.

Imaging studied by ultrasound and CT findings were very important to shift the diagnosis towards splenic tuberculosis. The imaging findings reported with splenic tuberculosis in their order of frequency are single or multiple hypoechoic focal lesions, splenic abscess, calcifications (on CT), and isolated splenomegaly. Ultrasound is not a sensitive tool to detect focal splenic lesions. In a study, five out of six patients with isolated splenomegaly on ultrasound were found to have lesions on CT.²¹ Recently, the wide use of PET/Scan as a tool for searching for metastasis in patient with malignancy, who already have low immunity due to the malignancy itself or its chemotherapeutic treatment, has leading to accidental diagnosis of splenic tuberculosis. Mostly in FDG PET/CT examination, spleen tuberculosis is seen as

multiple lesions with increased FDG uptake.²²

In our case the abdominal ultrasound was the only imaging technique used, and it showed splenomegaly without focal lesion. This of course is not enough to exclude presence of splenic nodules especially micronodules which would be detected if a CT scan had been used.

Real-time PCR is a very useful investigation for directly detecting the tubercle bacilli in clinical specimens.⁷ Detection of *Mycobacterium tuberculosis* by XpertMTB/Rif assay in splenic aspirate, splenic tissues, or abscess fluid would confirm the diagnosis of tuberculosis.^{7,12} However, Sahoo et al in their review has found that 26 case out of 31 was diagnosed histopathologically and only 5 patients were diagnosed by direct detection of mycobacterium.¹² Therefore, histopathological examination is necessary for aetiological diagnosis. Histopathologically, tuberculous infection can be identified by presence of typical caseation along with granuloma of epithelioid cells and Langhans giant cells.⁶

In our case, Real-time PCR or XpertMTB/Rif assay were not used the diagnosis of tuberculosis in ascetic fluid because the TB was not highly suspected at that time and the diagnosis was raised after finding of caseating active granulomas with Langerhans giant cells. And probably this is the message that we want to send to our colleagues to think of extrapulmonary tuberculosis even in the rare sites whenever we encountered a nonspecific presentation and to broaden our differential diagnosis list to include it.

Purified protein derivative is a marker of the diagnosis of latent tuberculosis but not active tuberculosis. It is reported to be positive in patients with splenic tuberculosis.²⁰ However, tuberculin skin test was performed in our case and it was negative.

The first line treatment of splenic tuberculosis is anti-tuberculous drugs for at least 6 months with 4 drugs in the initial phase and two in the following maintenance phase.^{20,23} this attitude is still recommended even after total splenectomy.³ In our patient the spleen was already removed and we started her on full anti-tuberculous therapy for 6 months. She responded nicely and fortunately without any adverse effects.

CONCLUSION

Yes, it is possible to encounter a patient with splenic tuberculosis during our career that TB is still a possible cause of splenomegaly and the patient should be treated with full course of anti TB medication even after splenectomy.

REFERENCES

1. People-centred framework for tuberculosis programme planning and prioritization, WHO, 2019.
2. Fooladi AAI, Hosseini MJ, Azizi T. Splenic tuberculosis: a case report. *Int. J. Infect. Dis.* 2009;13(5):273–275.
3. Johanna V. Basa, Lilly Singh, Wassim Abi Jaoude, Gainosuke Sugiyama. A case of isolated splenic tuberculosis. *International Journal of Surgery Case Reports* 2015;8:117–119.
4. Azzam NA. Splenic tuberculosis presenting as fever of unknown origin with severe neutropenia. *Annals of Clinical Microbiology and Antimicrobials* 2013;12(1):13. <https://doi.org/10.1186/1476-0711-12-13>
5. Masoodi I. Splenic tuberculosis: Report of two cases and literature review. *British Journal of Medical Practitioners*, 2017;10(1): 20-23.
6. Amin MA. Splenic Tuberculosis - A Rare Case Report. *Glob J Medical Clin Case Rep* 2017;4(3):072-073.
7. Kumar A, Kapoor VK, Behari A and Verma S. Splenic tuberculosis in an immunocompetent patient can be managed conservatively: a case report. *Gastroenterology Report*, 2018;6(1),72–74.
8. Lin SF, Zheng L and Zhou L. Solitary splenic tuberculosis: a case report and review of the literature. *World Journal of Surgical Oncology* 2016;14:154.
9. Pramesh CS, Tamhankar AP, Rege SA, Shah SR. Splenic tuberculosis and HIV-1 infection. *Lancet* 2002; 369(9303):353.
10. Sharma SK, Mohan A. Extrapulmonary tuberculosis. *Indian J Med Res* 2004;120: 316-353.
11. Paris S, Weiss SM, Ayers WH, et al. Splenic abscess. *Am Surg* 1994;60:358-61.
12. Sahoo S, Naik S, Mishra B, Durgeshwar G, Panigrahi MK, Bhuniya S. Tuberculous splenic abscess in the immunocompetent host: a report and review of literature. *Monaldi Archives for Chest Disease* 2020; 90:79-85.
13. Reichel C, Theisen A, Rockstroh JK, Müller-Miny H, Spen-gler U, Sauerbruch T. Splenic abscesses and abdominal tuberculosis in patients with AIDS. *Z-Gastroenterol* 1996; 34(8):494–6.)
14. C.S. Ajithkumar, Tuberculosis of spleen: case report. *Indian J Basic Appl. Med.Res.* 2013;6(2):619–622.
15. Dixit R, Arya MK, Panjabi M, et al. Clinical profile of patients having splenic involvement in tuberculosis. *Indian J Tuberc* 2010; 57:25-30.
16. Lim J, Yu JS, Hong SW, et al. A case of mass-forming splenic tuberculosis: MRI findings with emphasis of diffusion weighted imaging characteristics. *J Korean Med Sci* 2011; 26:457-60.
17. Mazloom W, Marion A, Ferron C, Lucht F, Mosnier JF. Tuberculose splénique: a partir d'un cas et revue de la littérature.

- Medecine et Maladies Infectieuses* 2002; 32:444–6.
18. Rhazal F, Lahlou MK, Benamer S, Daghi JM, Essadel E, Mohammadine E, et al. Splenomegalie et pseudotumeur splénique d'origine tuberculeuse: six nouvelles observations. *Ann Chir* 2004; 129:410–4.
 19. Hamzah R, Rohana AG, Anwar SA, Ong TZ, Hamazaini AH, Zuikarnaen AN. Splenic tuberculosis presenting as pyrexia of unknown origin. *Med J Malaysia* 2007;62(1):70–1.
 20. Berady S, Rahbi M, Bahrouch L, Sair K, Benzaine H, Benkirane A, et al. La tuberculose splénique pseudotumorale. *La Revue de Medecine Interne* 2005;26: 588–91.
 21. Sharma SK, Smith-Rohrberg D, Tahir M, Mohan A, Seith A. Radiological manifestations of splenic tuberculosis: a 23-patient case series from India. *Indian J Med Res*. 2007 May;125(5):669-78.
 22. Cegla P, Szychala A, Marszałek A, Wierchowska E, and Cholewinski W. Atypical spleen tuberculosis in a melanoma patient accidentally detected during a ¹⁸F FDG PET/CT study: Case report. *Molecular and Clinical Oncology* 2018;8: 89-92.
 23. Kumar S, Ajay G. Pai, Pravin N. Tungenwar, Ajay H. Bhandarwar. Isolated primary tuberculosis of spleen—A rare entity in the immuno-competent patient. *International Journal of Surgery Case Reports* 2017;30:93–96.



Abbreviations list: Centimetre (cm), Computed tomography (CT), Degree Celsius (°C), Fluorodeoxyglucose-positron emission tomography. (FDG PET/CT), Glutamic oxaloacetic transaminase (GOT), Glutamic pyruvic transaminase (GPT), Human immunodeficiency virus (HIV), Milligram (mg), Polymerase chain reaction (PCR), Positron Emission Tomography (PET), Red blood cells (RBCs), Tuberculosis (TB).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this case presentation a part from self funding.

PART 1 | IMAGING IN CLINICAL PRACTICE

Radiological findings of COVID-19: When to consider?

Nawal Jassar Al Khafagi*

ABSTRACT

Over the last 6 months, the world has been attacked by a new infection; COVID-19. Respiratory system is the main site of attack. Although the majority of those infected have relatively mild symptoms, many may pass into pneumonia and evolved into respiratory failure and death. The radiological findings in COVID-19 may be nonspecific and have similarities with other infectious and noninfectious diseases. In this article, we will try to go through the important radiological features and what findings should trigger thinking of it based on the updated recommendations of international radiology societies especially the British Society of Thoracic Imaging. We have to keep in mind that correlation of radiological findings with the clinical presentation and other laboratory tests is the best approach to reach the correct diagnosis.

Key words: COVID-19, GGO, Chest CT scan.

In December 2019 a pneumonia of unknown cause was detected in Wuhan in China and first reported to the WHO on 31 December 2019. WHO has declared a Public Health Emergency of International Concern on 30 January 2020 and a pandemic on 11 March 2020. The disease was found to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and named by WHO as COVID-19.¹ Progressively, the disease has distributed all over the world. About 5.2 million infections and 337000 deaths are reported in 216 countries, areas, and territories till 24 May 2020.²

It has a high infectivity rate with variable mortality rates among countries. The clinical presentation is diverse ranging from completely asymptomatic or mild nonspecific symptoms in 80 % of patients, to symptoms of lower respiratory tract infection necessitating hospital admission in about 20 %. In 5 % of patients the symptoms were very severe that need intensive care unit (ICU) admission. The case fatality rate is ~2-3 %.^{3,4}

Molecular testing is required to confirm the diagnosis for SARS-CoV-2. The real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test is used for this purpose, it is highly specific with a sensitivity of about 60-

70 %, but can give negative results initially.^{5,6} Other ancillary laboratory findings are also reported but they have prognostic rather than diagnostic significance, of these are lymphopenia, increased prothrombin time, lactate dehydrogenase, troponin and some inflammatory markers like CRP, ESR, and IL6.⁷

Role of imaging in the diagnosis and management of patients with COVID 19

- Add to pre-test probability assessment for COVID-19
- Distinguish between severe and non-severe cases.
- Look for an alternative diagnosis.
- Assess deterioration or discordant clinical course
- Assess complications.

Things to remember when dealing with Imaging of patients with COVID-19:

1. Clinical suspicion of COVID-19 is IMPERATIVE; otherwise, the radiology is nonspecific and could easily represent so many other pathological processes.⁶
2. While routine screening CT scan for the identification of COVID-19 pneumonia is currently not recommended by most radiol-

* MBChB, DMRD, FJMC, FRCR (UK), M Med in diagnostic radiology (NUS/Singapore). General Radiologist at Croydon University Hospital /London /UK. E mail: n_jassar2@yahoo.com, nawal.alkhafagi@nhs.net.

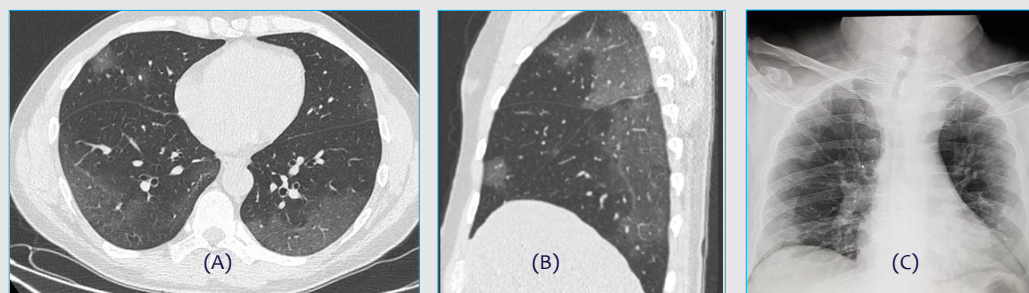


Figure 1 | Axial (A) and sagittal (B) sections of a CT scan of the chest of a patient with COVID-19 showing the classic category of COVID-19 (early stage). Patchy and bilateral GGO involving all lobes mainly the lowers. (C) chest X ray of another patient with early COVID-19 shows bilateral and peripheral opacities.

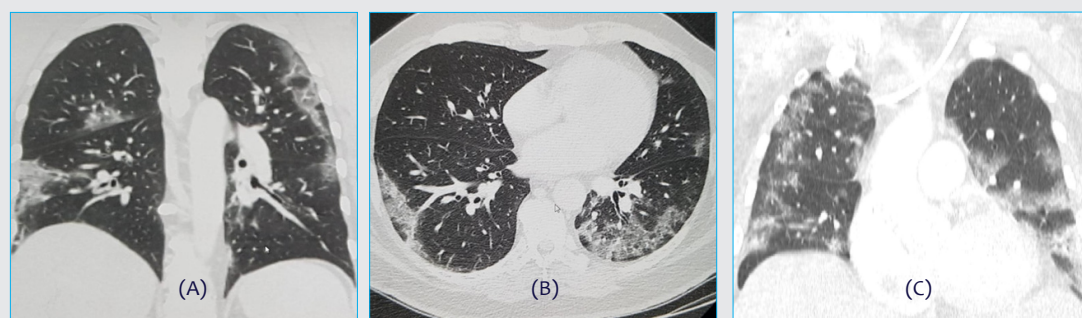


Figure 2 | A coronal (A) and axial (B) sections of a CT scan of a patient with COVID-19 shows bilateral peripheral patchy opacifications. (C) A coronal section of another patient showing the same features.

ogy societies, the number of CT scans performed in patients under investigation for COVID-19 has increased, CT scan play a role in the diagnosis of COVID-19 when the patient is seriously ill or PCR is unavailable.⁸

3. A standardized language should be followed to reduce the reporting variability and to improve communication with the referring providers.^{6,8}
4. Normal CT scan does not reliably exclude COVID 19 pneumonia in early stage. Initially CT scan of the chest is normal in 50 % after 2 days of symptoms but only in 4 % after 6-12 days.⁹

THE BSTI CATEGORIES

British Society of Thoracic Imaging (BSTI) has proposed four categories⁶ for the suggested standardized CT reporting language of COVID-19 based on current literatures and expert consensus.

Classic COVID-19 (100% confidence for COVID)

Features: Lower lobe predominant, peripheral

predominant, multiple, bilateral foci of ground glass opacities (GGO) $\pm$ crazy-paving, peripheral consolidation, air bronchogram and reverse halo/perilobular pattern (ie organizing pneumonia pattern).

H1N1 influenza, cytomegalovirus pneumonia, and other atypical pneumonias¹⁰ can have

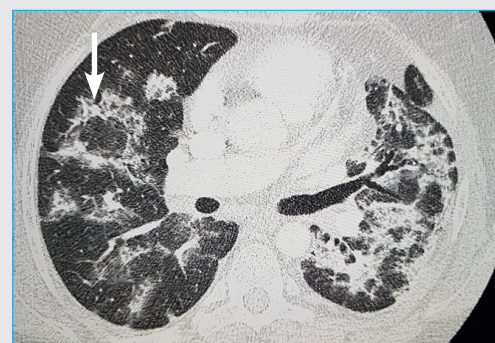


Figure 3 | Cross section chest CT scan below the bifurcation of trachea of a patient with COVID-19 shows bilateral opacifications, round and irregular, typical of organizing pneumonia, located at perilobular and peripheral areas. The arrow points to the reverse halo signs (atoll sign); A central lucency surrounded by an opacity.

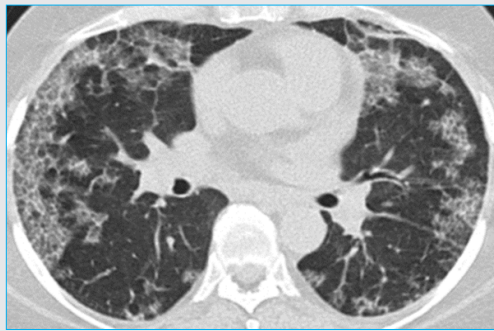


Figure 4 | Axial section of a CT scan of a patient with COVID-19 showing prominent interlobular and intralobular septal thickening on a background of bilateral, multifocal and peripheral GGO; features of crazy paving.

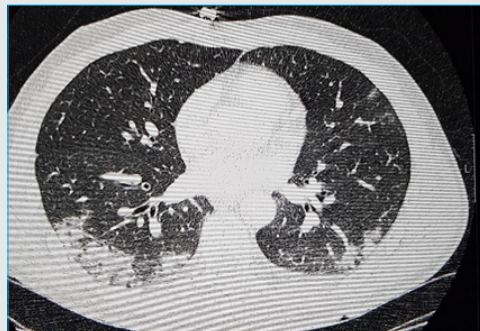


Figure 5 | Axial section of a CT chest of a patient with COVID-19 show bilateral confluent opacities seen on the periphery of the lower lobes.

similar findings. **See figure 1 a,b,c.**

Probable COVID-19 (71-99 % confidence for COVID-19)

Features: Lower lobe predominant mix of bronchocentric and peripheral consolidation, Reverse halo /perilobular pattern, but here GGO is scarce.

These features are nonspecific and can occur in a variety of infectious and noninfectious diseases. Clinical and other laboratory correlations are needed in such cases. **See figures 2, 3, 4, and 5.**

Indeterminate COVID-19 (< 70 % confidence for COVID-19)

Features: when the radiological picture Does

not fit into definite, probable, or non COVID-19. Or manifests above patterns but the clinical context is wrong or suggest an alternative diagnosis e.g an interstitial lung disease in a connective tissue disease. **See figure 6**

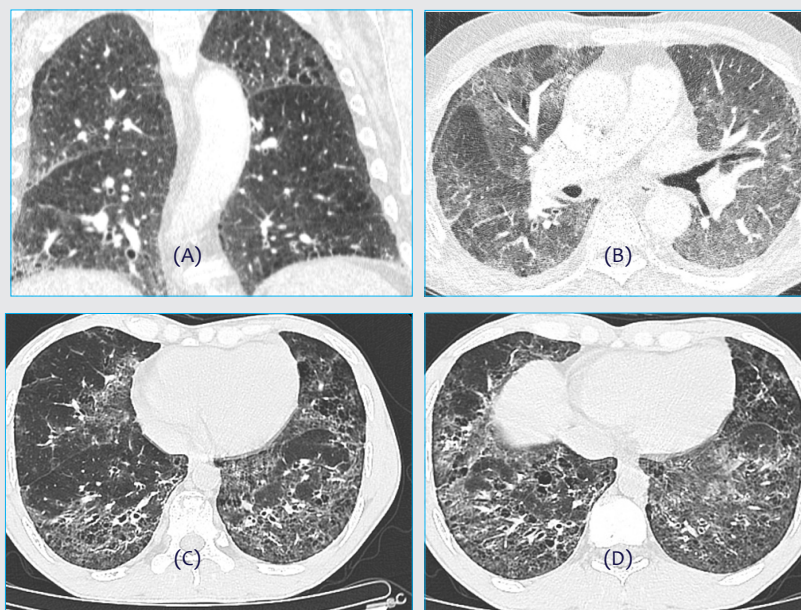
Clinical and other laboratory correlations are also needed in such cases.

Non-COVID-19 (70% confidence for alternative)

Features: Lobar pneumonia, cavitating infections, tree in bud/centrilobular nodularity, lymphadenopathy, effusions, established pulmonary fibrosis.

Such findings usually refer to a diagnosis other than COVID-19; however, we should not ignore the concomitant occurrence of COVID-19.

Figure 6 | CT chest of patients with indeterminate pattern of COVID-19: (A) and (B); coronal and axial images show diffuse ground glass opacity (GGO) in a patient with combined pulmonary fibrosis and emphysema. (C) and (D) axial images of a patient with systemic lupus erythematosus (SLE) show complex patterns, a GGO admixed with fibrotic lung changes and honeycomb appearance.



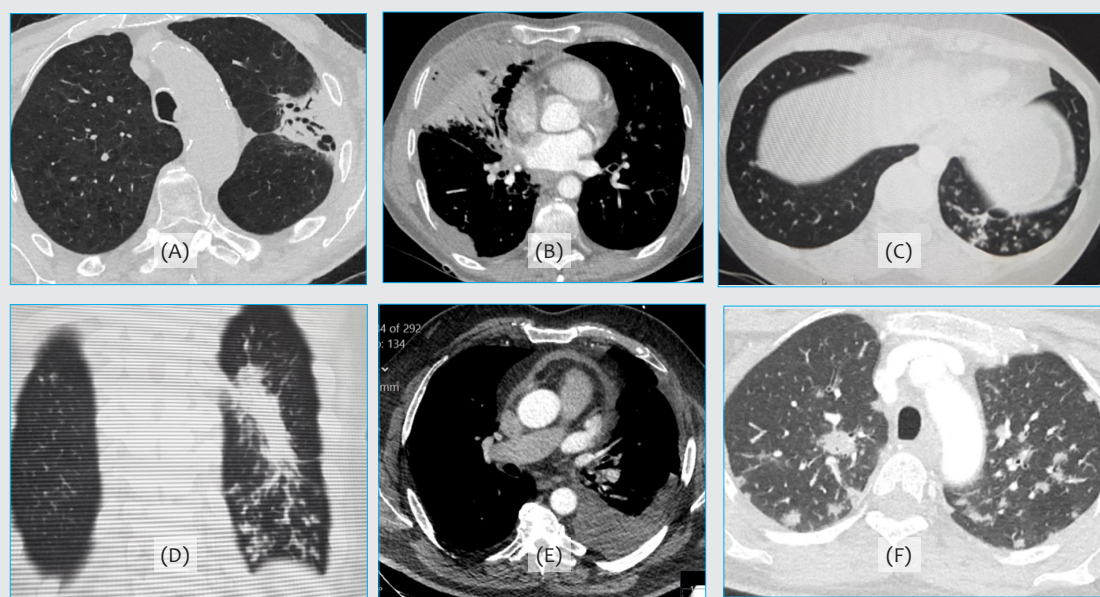


Figure 7 | CT pictures of different patients represent example of non COVID-19. (A) and (B) show a consolidation lesions with obvious air bronchogram suggestive of lobar pneumonia. (C) and (D) show centrilobular nodules in the left lower lobe with tree in bud appearance suggestive of infectious bronchiolitis. (E) shows left pleural effusion and (F) shows multiple and bilateral nodules.

ID-19 with other pathologies like heart failure or preexisting diffuse lung diseases which make the patient vulnerable to contract COVID-19 or have a severe form of it. Examples for non COVID-19 pattern **See figure 7.**

Complications of COVID-19 reported on chest imaging:

1. Pulmonary embolism and thrombosis in COVID-19 the European Society of Radiology and the European Society of Thoracic imaging suggested that contrast-enhanced CT should be performed to rule out pulmonary embolism if supplementary oxygen is needed in COVID-19 pneumonia patients with limited disease extension.¹¹ In a study in France about 50 % of Hospitalized patients who had respiratory deterioration with more need for oxygenation were found by CTPA to have pulmonary embolism.¹² **See figure 8**
2. Superadded bacterial infection represented by the development of pleural effusion and / or empyema. In a study, ventilator-associated pneumonia occurred in 10 of 32 patients (31%) with COVID-19 requiring invasive mechanical ventilation.¹³ **Figure 9**
3. Rapid progression to acute respiratory dis-

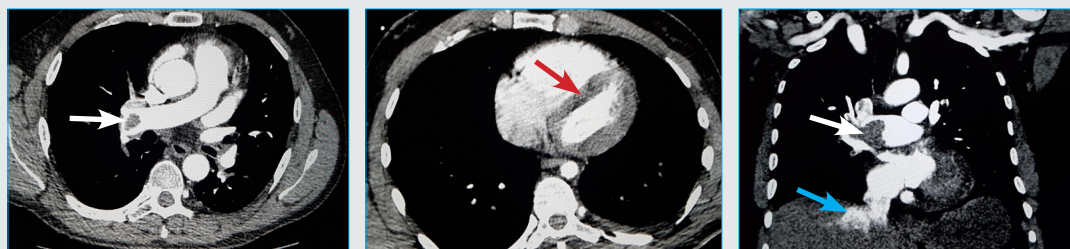


Figure 8 | CT pulmonary angio mediastinal window of a patient with COVID-19 and significant O₂ desaturation. (A) and (B) are axial sections while (c) is a coronal section. A & C show a filling defect (white arrows) in the right main pulmonary artery with early visualization of the inferior vena cava (blue arrow) due to reflux indicating high right ventricular pressure. The interventricular septum is pushed to the left ventricle in (B) (red arrow) due to increase right ventricular pressure.



Figure 9 | Axial section of a CT chest of a patient with COVID-19 shows left pleural effusion with patchy opacities more on the right lower lobe due to superadded bacterial infection (proved by bacteriological examination).

Figure 10 |

Severe COVID-19 patient admitted to ICU because of respiratory failure. (A) AP chest X-rays shows bilateral diffuse alveolar shadowings with good position of central venous line (white arrow), ET tube (red arrow) and NG tube (blue arrow). (B) Coronal CT image of the chest shows diffuse bilateral coalescent opacities and consolidation in the background of GGO.

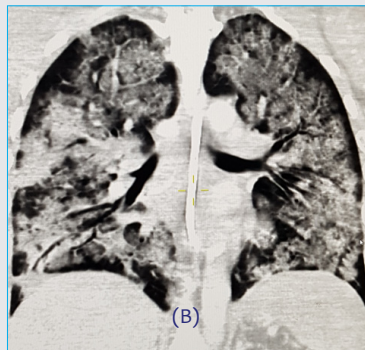
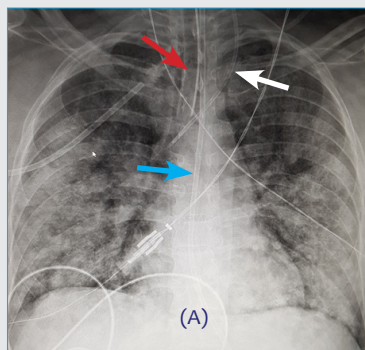
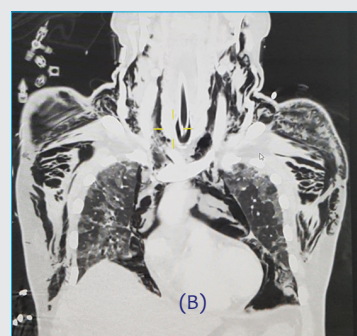
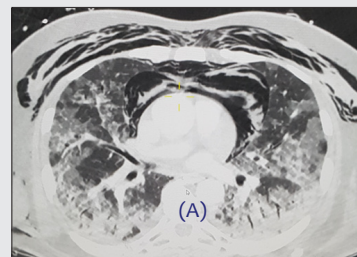


Figure 11 | Coronal section of a chest CT scan of evolving fibrosis in a patient with COVID-19 pneumonia (after 5 weeks of admission) shows linear and irregular diffuse opacities with reverse halo sign suggestive of organizing pneumonia pattern. Areas of reticulation and traction bronchiectasis are seen in left upper lobe (arrow).

Figure 12 | (A) axial section and (B) coronal section of a CT scan of the chest of a patient with COVID-19 show huge surgical emphysema and pneumomediastinum extended to the neck on a background of GGO with some consolidation and air trapping. A complication of invasive ventilation.



tress syndrome (ARDS). ARDS is a recognised complication of COVID-19 and it may occur rapidly over few hours to few days and usually carries a bad prognosis. **See figure 10**

4. Interstitial fibrosis can evolve in patient with COVID-19 pneumonia or a sequelae of ARDS. Some have reported lung fibrosis as a complication of severe COVID-19 as early as 2 weeks.¹⁴ Currently, there is no evidence that indicates the scarring in the

lungs experienced by COVID-19 patients is progressive.¹⁵ **See figure 11**

5. Surgical and mediastinal emphysema. It is usually iatrogenic and seen in ICU patient due to intubation or as a complication of artificial ventilation. This is not uncommon complication in ICU. In a study conducted in a tertiary centre in the UK, five patients developed pneumomediastinum within 7 days. Two of them had passed away.¹⁶ **See figure 12**

CONCLUSION

The radiological findings in COVID-19 may be nonspecific and have similarities with other infectious and noninfectious diseases, so radiological features should be correlated with the clinical findings and laboratory tests. Peripheral, bilateral, and multiple lower lobe predominant GGO is the classic features of COVID-19. While bronchocentric and peripheral consolidations with scarce GGO are features of probable infection.

REFERENCES

1. WHO. Events as they happen. Updated 19 May 2020, available at: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>.
2. WHO. Coronavirus disease (COVID-19), Situation Report – 125, 24 May 2020. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200524-covid-19-sitrep-125.pdf?sfvrsn=80e7d7f0_2.
3. Bell DJ. Covid 19. Radiopedia. Available at: <https://radiopaedia.org/articles/covid-19-3?lang=gb>.
4. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua liu xing bing xue za zhi* 2020;41(2):145-151. doi:10.3760/cma.j.issn.0254-6450.2020.02.003.
5. Kim H, Hong H, Yoon SH. Diagnostic performance of CT and reverse transcriptase-polymerase chain reaction for coronavirus disease 2019: a meta-analysis. *Radiology*. 2020 Apr 17:201343.
6. British society of thoracic imaging. Updated Version 2 BSTI COVID-19 Guidance For The Reporting Radiologist. Available at: https://www.bsti.org.uk/media/resources/files/BSTI_COVID-19_Radiology_Guidance_version_2_16.03.20.pdf. Accessed 20 May 2020.
7. Kermali M, Khalsa RK, Pillai K, et al. The role of biomarkers in diagnosis of COVID-19: a systematic review. *Life Sci*. 2020 May 13:117788.
8. Simpson S, Kay FU, Abbara S, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA [published online ahead of print, 2020 Apr 28]. *J Thorac Imaging*. 2020. DOI: 10.1097/RTI.0000000000000524.
9. Rodrigues JCL, Hare SS, Edey A, et al. An update on COVID-19 for the radiologist - A British society of Thoracic Imaging statement. *Clin Radiol*. 2020;75(5):323-325. doi:10.1016/j.crad.2020.03.003.
10. Kooraki S., Hosseiny M., Myers L. Coronavirus (COVID-19) outbreak: what the department of radiology should know. *J Am Coll Radiol*. 2020 Feb 19;(20):30150-30152.
11. Revel M-P, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, Brady A. European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). COVID-19 patients and the radiology department - advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur. Radiol*. 2020.
12. Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with Covid-19 pneumonia. *Eur Respir J* 2020; in press. Available at: <https://doi.org/10.1183/13993003.01365-2020>.
13. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054-62.
14. Spagnolo P, Balestro E, Aliberti S, Cocconcini E, Biondini D, Giovanni Della Casa G, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? *The Lancet* May 15, 2020. Available at: [https://doi.org/10.1016/S2213-2600\(20\)30222-8](https://doi.org/10.1016/S2213-2600(20)30222-8).
15. Pulmonary Fibrosis Foundation. Fibrosis or pulmonary fibrosis? COVID-19 coverage leads to confusion. Edited on 4 May 2020. Available at: https://www.newswise.com/coronavirus/fibrosis-or-pulmonary-fibrosis-covid-19-coverage-leads-to-confusion/?article_id=730976. Accessed on 27 May 2020.
16. Wali A, Rizzo V, Bille A, Routledge T, Chambers A. Pneumomediastinum following intubation in COVID-19 patients: a case series [published online ahead of print, 2020 May 6]. *Anaesthesia*. 2020. doi:10.1111/anae.15113.



Abbreviations list: Acute respiratory distress syndrome (ARDS), British Society of Thoracic Imaging (BSTI), C Reactive protein (CRP), Computerized tomography (CT), CT pulmonary angiography (CTPA), Erythrocyte sedimentation rate (ESR), ground glass opacities (GGO), Intensive care unit (ICU), Interleukin 6 (IL6), Reverse transcriptase-polymerase chain reaction (RT-PCR), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), United Kingdom (UK), World Health Organization (WHO).

Conflict of interest: Authors have nothing to declare.

Funding: Authors received no funds to complete this educational article.

Acknowledgement: I would like to express by gratitude to the radiology department at Croydon University hospital in London UK especially the lead manager, Dr Ketul Patel and the IT department in particular the PACS manager, Ricky Lawless for their kind support and guidance.

PART 2 | WHAT DO YOU KNOW ABOUT

The pharmacologic management of heart failure and its co-morbidities: what is written in the guidelines?

Hilal B. Al-Safar*

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) caused by a structural and/or functional cardiac abnormality; ischemic heart disease is the commonest cause. Approximately 1–2% of the adult population in developed countries suffer from heart failure, rising to $\geq 10\%$ among people 70 years of age. Clinically, it is divided according to the NYHA functional classification into four severity levels. Based on ejection fraction (EF), heart failure is divided into HF with preserved ejection fraction (HFpEF) when $EF \geq 50\%$, HF with reduced EF (HFrEF) when $EF < 40\%$, and HF with a middle range EF (HFmrEF) when EF is in the range of 40–49%. This classification is of importance in terms of epidemiology, management, and prognosis. In this educational source, we are presenting important messages about the drug therapy of heart failure with treatment of some co-morbidities based on the latest ESC and AHA guidelines.

Questions

Q 1: Biomarkers screen in prevention of heart failure

A 55-year-old male patient presented to the outpatient department for checkup. He was hypertensive and diabetic for the last ten years on *lisinopril* 10 mg/day and *metformin* 1000 mg/day, asymptomatic for the time being. On clinical exam blood pressure is 145/90 mmHg and his HbA1c is 7%.

Which of the following statement is the most appropriate next step true?

- a) Give dietary advice and schedule for next visit.
- b) Increase the dose of *lisinopril* to 20 mg/day and *metformin* to 2000 mg/day.
- c) Add *statin* and *antiplatelet* to his medication.
- d) Ask for brain natriuretic peptide screen (BNP) and optimise guidelines directed management and therapy (GDMT).
- e) Being asymptomatic, no further action is needed.

Q 2: Drugs affect survival of patients with heart failure

All the following drugs improve survival in patients with HFrEF except:

- a) Beta blockers
- b) ACE inhibitors
- c) Loop diuretics
- d) Sacubitril
- e) Spironolactone

* MBChB, FRCP (UK), FACC. Consultant and assistant professor of cardiology. College of Medicine, Baghdad University, Iraq.
E mail: crescent1957@yahoo.com.

Q 3: Role of ARNI in patient with HFrEF

A 65-year-old female diagnosed as heart failure due to uncontrolled hypertension for many years asked your opinion about her medical therapy. She is a house wife doing most of her usual daily activities, during the last three months she noticed that her exercise capacity became more limited and now she gets tired with SOB for even going to bathroom. On clinical exam: BP 130/80 mmHg, HR 60 bpm regular with normal volume, JVP normal, normal cardiac auscultation, clear lung bases and no pedal oedema. Her current treatment includes: *ramipril* 5 mg/day, *indapamide* 1.5 mg/day, *carvedilol* 25 mg/day, *spironolactone* 25 mg/day. ECG showed LVH, Echocardiography showed EF 40%.

What will be the most appropriate step:

- Increase the dose of *ramipril* to 10 mg / day.
- Increase *spironolactone* to 50 mg /day.
- Replace *ramipril* by *valsartan/sacubitril* therapy.
- Start *torsemide* tab 10 mg /day
- Increase *carvedilol* to 50 mg /day.

Q 4: Drugs not indicated or harmful in heart failure

All these statements are false regarding drug therapy of HFrEF Except:

- ARBs are more effective than ACE inhibitors.
- To prevent the potential risk of thrombosis all patients should be kept on anticoagulation.
- Verapamil and *diltiazem* can be used safely in those patients to treat high blood pressure.
- Aspirin* is not indicated for patient with HFrEF unless in the presence of CAD.
- There is a growing role for statin in the treatment of patient with HFrEF.

Q 5: Indication for Ivabradine in heart failure

All of the following statement related to Ivabradine usage to reduce heart failure hospitalization are true Except:

- Maximum tolerated doses of GDMT beta blocker therapy should be in place before starting Ivabradine.
- NYHA class II-III.
- EF less than 35%.
- Should be in sinus rhythm .
- Heart rate should be less than 70 bpm.

Q 6: Iron deficiency anaemia in heart failure

During assessment of patient with heart failure ,the base line screen showed : Hb 10 mg/dl, blood urea 20 mg/dl, serum creatinine 0.9 mg /dl serum ferritin 30 ng/ml (normal value is 20-250 ng/ml for males and 10-120 ng/ml for females), the next step should be:

- Oral iron therapy as it showed improvement in quality of life (QoL).
- Parenteral iron therapy as it shoed improvement in QoL.
- Advice for iron rich diet only.
- Add oral multivitamin rich in iron.
- Subcutaneous erythropoietin stimulating agent.

Q 7: Hypertension in heart failure

A 55-year-old patient, presented to outpatient clinic because of being told that he was hypertensive. His mother died at the age of 50 years because of heart failure and his younger brother is hypertensive, he is currently heavy smoker and his fasting lipid profile showed total cholesterol of 320 mg/dl. On clinical exam his BP was 160/100 mmHg, the rest of exam was normal.

Which of the following statement related to BP target (office reading) that help in heart failure prevention is true ?

- a) BP target should be below 150/100 mm Hg
- b) BP target should be below 140/95 mm Hg
- c) BP target should be below 130/90 mm Hg
- d) BP target should be below 130/80 mm Hg
- e) BP target should be below 120/70 mm Hg

Q 8: Sleep disorder and heart failure

Sleep disorders are common in patients with heart failure, it was found that 61% of patients with heart failure had some sort of sleep disorder (central or obstructive sleep apnea) and therefore a formal sleep study should be conducted on suspicion.

Which of the following statement is true?

- a) In obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness.
- b) In obstructive sleep apnea, CPAP may be reasonable to improve survival.
- c) In patients with NYHA class II–IV HFrEF and central sleep apnea, adaptive servo-ventilation is appropriate therapy
- d) The management for both obstructive and central sleep apnea (CSA) is the same

Q 9: Diuretic therapy in patient with heart failure

A 60 year old patient who had been previously diagnosed as ischemic heart disease and heart failure, presented to the emergency department complaining from fatigue, SOB and orthopnea but no chest pain.

On clinical exam: Looks tired, anxious and in respiratory distress, couldn't lie flat, BP 110/80 mmHg, pulse 110 bpm normal volume, O2 sat 90% at room air, JVP 8cm above costal margin, cold extremities, soft S1 S2 and S3 gallop, no murmurs, bilateral basal crepitation. His current medication was: oral furosemide 80 mg/day, Enalapril 10 mg/day, spironolactone 25 mg/day, isosorbide dinitrate 20 mg /d day and carvedilol 25 m/d day.

Your decision was to admit the patient and start parenteral diuretic therapy, which of the following statement is true as regard to the initial dose?

- a) Start intravenous furosemide 40 mg twice daily
- b) Start intravenous furosemide 60 mg twice daily
- c) Start intravenous furosemide 80 mg twice daily
- d) Start intravenous furosemide 100 mg twice daily

Q 10: Management of patients with HFpEF

A 65-year-old lady who is known to be hypertensive and diabetic for the last 15 years consulted you because of progressive exercise intolerance and shortness of breath for the last six months. During the last week she started to have SOB on lying down and bilateral pedal oedema but there was no chest pain or palpitation and she was kept on *atenolol* 100 mg/day, *Glucophage* 1500 mg/day.

On clinical exam: BMI 28 kg/m², BP 160/105 mmHg, pulse 88 bpm, JVP 8 cm above sternal margin, normal S1, loud S2, S4, no murmur, few bilateral basal lung crepitation and ++ bilateral pedal oedema. Full laboratory testing was normal apart from HbA1c 8%, Pro BNP 80.0 pg/ml, and triglyceride 300 mg/dl. Echocardiography showed LV EF of 62%.

Which of the following statement related to this patient management is true?

- Heart failure is unlikely in this patient and we should look for alternative cause.
- Controlling both systolic and diastolic BP is priority in this patient management.
- Calcium channel blockers is the 1st line therapy to control this patient hypertension.
- Diuretics is of limited value in the management of this lady.
- Nutritional supplements is usually useful in this patient management.



Abbreviations list: American Heart Association (AHA), Angiotensin converting enzyme inhibitors (ACEI), Angiotensin receptor blockers (ARBs), Angiotensin receptor neprilysin inhibitor (ARNI), Beat per minute (bpm), Blood pressure (BP), Body mass index (BMI), Brain natriuretic peptide screen (BNP), Calcium channel blockers (CCBs), Central sleep apnea (CSA), Class of recommendation (COR), Continuous positive airway pressure (CPAP), Coronary artery disease (CAD), Cyclo-oxygenase 2 inhibitors (COX2 inhibitors), Ejection fraction (EF), Electrocardiography (ECG), European Society of Cardiology (ESC), Guidelines directed management and therapy (GDMT), Heart failure (HF), Heart rate (HR), HF with a middle range EF (HFmrEF), HF with preserved Ejection fraction (HFpEF), HF with reduced EF (HFrEF), Intravenous (IV), Jugular venous pressure (JVP), Left ventricular hypertrophy (LVH), Level of evidence (LOE), Mineralocorticoid receptor antagonist (MRA), New York Heart Association (NYHA), Non-steroidal anti-inflammatory drugs (NSAIDs), Obstructive sleep apnoea (OSA), Quality of life (QoL), Shortness of breath (SOB), Sleep-disordered breathing (SDB).

Explanation of classes of recommendation and level of evidence used in the answers of these questions

Class (strength) of recommendation (COR)		
	Class I	(Strong) Benefit >>> Risk. The intervention is recommended/ indicated/ useful/ effective.
	Class IIa	(Moderate) Benefit >> Risk. The intervention is reasonable
	Class IIb	(Weak) Benefit ≥ Risk. The intervention may be reasonable
	Class III	No benefit (moderate) Benefit = Risk. The intervention is not recommended
	Class III	Harm (Strong) Risk > Benefit. The intervention is potentially harmful
Level (Quality) of evidence (LOE)		
	Level A	High quality evidence of more than one RCT, or meta-analysis of such studies.
	Level B-R	Moderate quality evidence RCT or meta-analysis (Randomized)
	Level B-NR	Moderate quality non-randomized or observational studies. Or meta-analysis on such studies.
	Level C-LD	Limited data. R and non-R CT of limited design or their meta-analysis.
	Level C-EO	Expert opinion

Answers

Q 1: The correct answer is d

In addition to its useful role in supporting or excluding the diagnosis of heart failure, for patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team-based care, including a cardiovascular specialist optimizing guidelines directed management and therapy (GDMT) to address the risk factors, can be useful to prevent the development of left ventricular dysfunction (systolic or diastolic) or new-onset HF. Elevation of natriuretic peptide should be interpreted cautiously, because many cardiac and noncardiac conditions can increase it as well. Obesity may be associated with lower natriuretic peptide concentrations, and this may modestly reduce diagnostic sensitivity in morbidly obese patients. **Table 1** shows these conditions

New data suggest that natriuretic peptide biomarker screening and early intervention to control risk factor may prevent HF.

Table 1 Potential Causes of Elevated Natriuretic Peptide

Cardiac
HF, including RV syndromes
Acute coronary syndromes
Heart muscles disease, including LVH
Valvular heart disease
Pericardial disease
Atrial fibrillation
Myocarditis
Cardiac surgery
Cardioversion
Toxic-metabolic myocardial insults, including cancer chemotherapy
Noncardiac
Advancing age
Anaemia
Renal failure
Pulmonary: obstructive sleep apnea, severe pneumonia
Pulmonary hypertension
Critical illness
Bacterial sepsis
Severe burns

COR	LOE
Ia	B-R

Q 2: The correct answer is c

Neuro-hormonal antagonists [ACEIs, MRAs (mineralocorticoid receptor antagonist) and beta-blockers] have been shown to reduce hospitalization and death in patients with HFrEF and are recommended for the treatment of every patient with HFrEF, unless contraindicated or not tolerated. Angiotensin receptor neprilysin inhibitor (ARNI) like Sacubitril reduces the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA. Diuretics including loop diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion but not to change survival.

ACE inhibitors, beta blockers and Potassium-sparing diuretics should be used in every patient with HFrEF unless contraindicated or not tolerated.

ACEI, ARBs	I	A
ARNI	I	B-R
Beta blockers, MRA	I	A*

* ESC guidelines 2016/ acute and chronic heart failure.

Q 3: The correct answer is c

Neprilysin is an enzyme that degrades natriuretic peptides, bradykinin and other vasoactive peptides. Neprilysin inhibitor combined with an ARB (ARNI) reduces the CV mortality or HF hospitalization significantly in persistently symptomatic patient with HFrEF NYHA class II or III who is using ACEI.

ACE inhibitors, beta blockers and Potassium-sparing diuretics should be used in every patient with HFrEF unless contraindicated or not tolerated.

COR	LOE
I	B-R



Q 4: The correct answer is d

Verapamil / Diltiazem	III*	A
NSAIDs/ COX2 inhibitors	III*	B

* ESC guidelines 2016/ acute and chronic heart failure.

ARBs are recommended only as an alternative in patients intolerant of an ACEI. Anticoagulants are not used routinely in patients with HFrEF unless it is indicated for prevention of thrombosis like in atrial fibrillation or treatment of already existed thromboembolic disease for example pulmonary embolism. (CCBs) are not indicated for the treatment of patients with HFrEF. *Diltiazem* and *verapamil* have been shown to be unsafe in patients with HFrEF. There is only evidence on safety for *amlodipine* and *felodipine* in patients with HFrEF, and they can be used only if there is a compelling indication in patients with HFrEF. Although statins reduce mortality and morbidity in patients with atherosclerotic disease, they are not effective in improving the prognosis in patients with HFrEF.



Statins, antiplatelets, and anticoagulants are not routinely used unless indicated for another reason, while verapamil and diltiazem are harmful.



Q 5: The correct answer is e

COR	LOE
Ila	B-R

Ivabradine slows the heart rate through inhibition of the I_f channel in the sinus node and therefore should only be used for patients in sinus rhythm. It can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF < 35%) who are receiving guidelines directed management and therapy (GDEM), including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.



In HFrEF, *Ivabradine* therapy reduces hospitalization.



Q 6: The correct answer is d

COR	LOE
Iib	B-R

In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation is < 20%), intravenous iron replacement might be reasonable to improve functional status and QoL. Routine baseline assessment of all patients with HF includes an evaluation for anaemia in addition to other baseline laboratory measurements. Anaemia is independently associated with severity of HF disease, and iron deficiency appears to be uniquely associated with reduced exercise capacity. When iron deficiency is diagnosed and after full evaluation for cause, intravenous repletion of iron, may improve exercise capacity and QoL.



Proper treatment of Iron deficiency anaemia improves functional status and QoL in patient with heart failure.



Q 7: The correct answer is d

COR	LOE
I	B-R

In patients at increased risk, stage A HF, the optimal blood pressure in those with hypertension should be less than 130/80 mm Hg. Patients with HFrEF and HFpEF and hypertension should be prescribed GDMT titrated to attain systolic blood pressure less than 130 mmHg.



Blood pressure target for primary prevention of heart failure should be < 130/80 mmHg.

Q 8: The correct answer is a

Perform sleep study	Ila	C-LD
Use of CPAP	IIb	B-R
Servo-ventilation for CSA	III	B-R

Sleep-disordered breathing (SDB) occurs in about 60 % of patients with HF. The commonest are obstructive sleep apnoea (OSA) and central sleep apnoea (CSA). CSA and OSA have been shown to be associated with a worse prognosis in HF. OSA is associated with an increased risk of incident HF in men. In patients with NYHA class II–IV HF and suspicion of sleep-disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable. If OSA is diagnosed, CPAP may be reasonable to improve sleep quality and daytime sleepiness. In patients with NYHA class II–IV HF and central sleep apnea, use of adaptive servo-ventilation led to an increase in both all-cause and cardiovascular mortality.



Sleep study is indicated for patients with HF if there is suspicion of sleep disturbance or daytime somnolence.

Q 9: The correct answer is d

For example, for patients taking 40 mg of oral furosemide twice daily as an outpatient, initial intravenous (IV) dosing would be 100 mg of furosemide IV twice daily. For patients not receiving long-term loop diuretics agents, 40–80 mg IV BID of furosemide or the equivalent is a reasonable empiric starting dose. Due to post-dosing Na⁺ retention, IV loop diuretic agents should usually be given at least twice daily.



For patients with heart failure on long-term loop diuretic agents who were admitted to hospital after decompensation, 2.5 times their outpatient dose on a mg per mg basis, demonstrated safety and efficacy in the DOSE trial.

Q 9: The correct answer is b

Diuretics for volume overload	I	B
ACEI, B Blockers, ARBs	IIa	C

Blood pressure control in accordance with hypertension guidelines remains the most important recommendation in patients with HFpEF. Evidence from a randomised controlled trials has shown that improved blood pressure control reduces hospitalization for HF, decreases cardiovascular events, and reduces HF mortality in patients without prevalent HF. In hypertensive patients with HFpEF, aggressive treatment (often with several drugs with complementary mechanisms of action) is recommended. Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF. The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF.



Most of the recommended therapies for patients with HFpEF are directed at symptoms, especially comorbidities, and risk factors that may worsen cardiovascular disease.

REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Monica M, Colvin MM, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Journal of the American College of Cardiology*, 2017;70.6: 776-803.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. Authors/Task Force Members; Document Reviewers (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*, 2016;18(8): 891-975.
3. Felker G, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9):797-805. doi:10.1056/NEJMoa1005419

