Original Article

TANAFFOS

A Theoretical Death Map of Patients with COVID-19: A Single Center Experience

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Background: Given the increase in mortality from COVID-19 disease, understanding the causal chain leading to death in patients with this disease will be of particular importance. This study aimed to draw the death map of patients with COVID-19 in BESAT hospital (West of Iran), based on investigating the underlying, intermediate, and terminal causes of death in this group of patients.

Materials and Methods: To draw the death map of patients with COVID-19 in this cross-sectional study, the death certificate and medical records of 183 COVID-19 patients who died at BESAT Hospital in Hamadan (West of Iran) in 2020 were reviewed. The cases in which the underlying cause of death was COVID-19 were reviewed. A checklist was used to collect the data. It was designed based on the international form of medical certificate of cause of death (issued by WHO). The collected data were analyzed by SPSS software version 23.

Results: The most prevalent underlying causes of death were COVID-19 (60.7%), COVID-19-related pneumonia (19.1%), acute respiratory distress syndrome (10.9%), and severe sepsis (9.8%). Hypertension (8.2%), diabetes (6.0%), seizures (3.8%), and ischemic heart disease (2.2%) were the most influential conditions affecting death. The number of deaths due to the terminal cause of acute respiratory distress syndrome in women (22.5%) was much higher than in men (7.1%) (P-value=0.041). Findings indicated that most patients died from four main pathways originating from COVID-19, leading to causes such as sepsis, ARDS, myocarditis, MI, and PTE.

Conclusion: The results indicate that health officials and healthcare providers should be able to identify and monitor patients with chronic diseases and implement effective plans to prevent COVID-19. Physicians should also take important steps in offices, clinics, and hospitals, such as conducting early echocardiography in children, providing respiratory support, and preventing deep vein thrombosis in adults during hospitalization. It is also essential to inform the public through audio and video media, including radio and television.

Keywords: COVID-19; Death etiology; Death certificate; Death map

INTRODUCTION

Death is the complete cessation of the vital functions of the body without return. According to studies, in most developing countries, cardiovascular diseases, traffic accidents, and cancers are the three most common causes of death (1-3). Infectious diseases, however, are still one of the oldest enemies of human life. Despite significant advances in medical science for preventing and treating

infectious diseases, the potential for epidemics remains a global issue (4).

Emerging diseases such as cholera, plague, and yellow fever, which have caused widespread fatalities worldwide, have become more prevalent and complex (5). The outbreak of COVID-19 occurred in December 2019. The disease originated in China and spread rapidly (6). According to the World Health Organization (WHO) statistics, more than 167,492,769 cases of infection and 3,482,907 cases of death (until May 26, 2021) have been reported so far (7).

Coronaviruses multiply in the body of animals, and some of them can be transmitted from animals to humans while most cause respiratory symptoms. Other symptoms include fever, cough, sore throat, shortness of breath, fatigue, and lethargy (4).

With the announcement of the WHO, COVID-19 was known as an epidemic. Accordingly, the increase in virus-related deaths around the world has highlighted the importance of accurate data in confirming these fatalities (6). Based on the WHO sources in 2003, about 90% of developed countries had a complete mortality registration system, while about 10% of the third-world countries had this system (7). The basis of mortality data is the medical certificate of cause of death (death certificate) (8). According to the lines related to the causes of death in the international form of medical certificate of cause of death (death certificate), the underlying cause, intermediate causes, and the terminal or direct cause of death can be identified. This will make it possible to know the process of the death of patients to some extent (9).

Concerning WHO opinion, the underlying cause of death is an illness or injury that triggers a series of disease events that are directly related to death, or a condition that has led to fatal injury and poisoning. The intermediate causes of death in the chain of events leading to death are one or a set of causes that are the connection between the underlying cause and the terminal cause. In other words, these causes become a means to lead the underlying cause to the terminal cause. The terminal or direct cause of death is an illness, injury, or complication that directly causes death, and therefore forms the first line in the chain

leading to death. In the present study, the death map or theoretical death map of COVID-19 patients is a set of the underlying intermediate and terminal causes that lead to the patient's death (9,10).

Mortality statistics systems with reliable data on the cause of death are the main source for effective health planning (11,12). Given the increased mortality from COVID-19 disease, understanding the chain of causes leading to death in patients with this disease will be of particular importance. Accordingly, this study aimed to draw the death map of patients with COVID-19 in BESAT hospital (west of Iran) investigating the underlying intermediate and terminal causes of death of this group of patients.

MATERIALS AND METHODS

The final goal of the present study was to draw a theoretical map of the COVID-19 mortality. To draw this map, the researchers examined the death certificates and medical records of patients who died due to the COVID-19 disease. For this purpose, a cross-sectional descriptive study was designed. In this study, the research population was patients who died from the COVID-19 disease in BESAT Hospital in Hamadan (west of Iran) in 2020.

Inclusion criteria were patients with COVID-19 confirmed by positive PCR or pulmonary evidence of COVID-19 infection (the second case was considered based on the diagnoses of medical records). Exclusion criteria were the incomplete death certificate in the patient's medical records and the impossibility of completing the information. In the study, the Medical records of 204 deceased COVID-19 patients in BESAT Hospital were reviewed. 21 patients were excluded from the study due to a lack of enough information and deficiencies in the death certificates. Finally, the medical records and the death certificates of 183 deceased COVID-19 patients were analyzed.

In our study, the basis for designing and drawing the death map of patients with COVID-19 was paying attention to the diseases and conditions recorded in the cause of death section of the death certificate of these patients. As we know, in the international death certificate published by the World Health Organization, two parts are

designed to record the causes of death. The first part includes four lines including lines a, b, c and d. The second part includes other factors involved in death (Figure 1) (9). In the present study, the four lines in the first part of the death certificate were considered in order to draw the death map of patients suffering from COVID-19. The conditions recorded in the second part and other conditions written in the medical records of these patients were considered as predisposing factors.
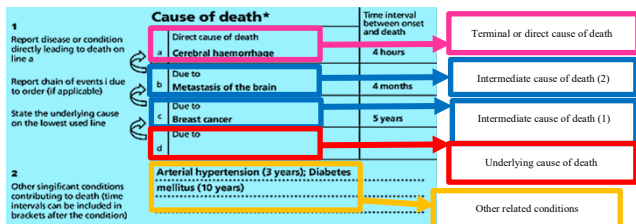

Figure 1. The international death certificate form-cause of death section

A checklist was used to collect the necessary data including mortality data and other supplementary data. The checklist was designed based on the international form of medical certificate of cause of death (issued by WHO), which consisted of three parts (9). The first part of the checklist evaluated the demographic data. The second part dealt with the main information on the causes of death. In this section, the underlying, intermediate, and the terminal causes leading to deaths were identified. The third section was dedicated to recording other medical information such as a history of surgery or underlying diseases. Necessary data were extracted from the Health Information Management Department of BESAT Hospital with the coordination of the head of the hospital information system. Also, to complete the data collection process, the medical records of patients with COVID-19 were retrieved and studied. From the medical records, some forms were reviewed including the admission and discharge summary, clinical history, and death certificate.

Finally, the completed checklists were coded. Data analysis was performed using SPSS software version 23 with descriptive and analytical statistics. Mean, standard deviation, frequency, and percentage in tables and graphs were used to describe the data. A Chi-square test was used to compare the causes of death in patients according to demographic characteristics including gender, marital status, and place of residence. The significance level was considered at 0.05.

RESULTS

In the study, the medical records and the death certificates of 183 deceased COVID-19 patients in BESAT hospital were reviewed. According to the demographic characteristics of the research population, the mean age of the population was 56.1 years with a standard deviation of 22.1 years. The oldest was 96 years old and the youngest was 3 months old. 61.2% of the dead patients were male and 38.8% were female while most of them were married (74.7%). Also, 60.6% of the dead patients lived in the urban and 39.4% in the rural area.

According to Table 1, the most important underlying causes of death were COVID-19 (60.7%), loss of consciousness (9.8%), and intracerebral hemorrhage (7.1%), respectively.

Table 1. Frequency distribution of the underlying cause of death in the research population

Row	Underlying cause	No	%
1	COVID-19	111	60.7
2	Decreased consciousness	18	9.8
3	Intracerebral hemorrhage	13	7.1
4	High blood pressure	7	3.8
5	Falling down	5	2.7
6	Chemotherapy	5	2.7
7	Femoral fracture	5	2.7
8	Immunodeficiency	4	2.2
9	Myocardial infarction	1	0.5
10	Coronary artery bypass grafting (CABG)	2	1.1
11	Throat cancer	1	0.5
12	Chest trauma	1	0.55
13	Pill poisoning B2	1	0.55
14	Hodgkin's lymphoma	1	0.55
15	Lung cancer	1	0.55
16	Ewing sarcoma	1	0.55
17	DVT	1	0.55
18	Intestinal perforation	1	0.55
19	Neonatal hemolytic disease (HDN)	1	0.55
20	Brain mass surgery	1	0.55
21	Methadone poisoning	1	0.55
22	Uterine and ovarian cancer	1	0.55
Total		**164**	**89.6**

Table 2. Shows that the most important first intermediating causes of death were COVID-19-insduced pneumonia (13.1%), loss of consciousness (8.2%), and deep vein thrombosis (3.8%), respectively

Row	The first intermediate cause of death	No	%
1	COVID-19 pneumonia	24	13.1
2	Decreased consciousness	15	8.2
3	DVT(deep vein thrombosis)	7	3.8
4	Immunodeficiency	4	2.2
5	Plural effusion	4	2.2
6	Renal failure (ESRD)	4	2.2
7	Chemotherapy	4	2.2
8	Dialysis	2	1.1
9	Myocarditis	2	1.1
10	Prematurity	2	1.1
11	Aortic aneurysm	2	1.1
12	subarachnoid hemorrhage	2	1.1
13	Intracerebral hemorrhage (ICH)	2	1.1
14	Metastasis	2	1.1
15	Hemothorax	2	1.1
16	Choroidal neovascularization	2	1.1
17	Cerebral aneurysm	2	1.1
18	myocardial infarction	2	1.1
19	Hypocalcemia	2	1.1
20	Sepsis	2	1.1
21	Intubation	2	1.1
22	Cerebellar hemorrhage	2	1.1
Total		**92**	**50.2**

Also, most important second intermediating causes of death were COVID-19-insduced pneumonia (8.2%), pneumonia (3.8%), and deep vein thrombosis (3.8%), respectively (Table 3).

Table 3. Frequency distribution of the second intermediate cause of death in the research population

Row	the second intermediate cause of death	No	%
1	COVID-19 pneumonia	15	8.2
2	Pneumonia	7	3.8
3	DVT	7	3.8
4	Decreased consciousness	7	3.8
5	Peritonitis caused by intestinal obstruction	4	2.2
6	Sepsis	4	2.2
7	Severe cardiopulmonary involvement	2	1.1
8	Mesenteric ischemia	2	1.1
9	Acute myeloblastic leukemia (AML)	2	1.1
10	Metastasis	2	1.1
11	Plural effusion	2	1.1
12	Ileus	2	1.1
13	Acute Respiratory Distress Syndrome (ARDS)	2	1.1
14	Hospitalization in the ICU	2	1.1
Total		**60**	**32.7**

According to Table 4, most important terminal causes of death were pneumonia (19.1%), acute respiratory distress syndrome (10.9%), and severe sepsis (9.8%), respectively.

Table 4. Frequency distribution of terminal cause of death in the research population

Row	Terminal Cause of Death	No	%
1	Pneumonia	35	19.1
2	Acute Respiratory Distress Syndrome (ARDS)	20	10.9
3	Sepsis	18	9.8
4	Pneumonia	15	8.1
5	Myocardial infarction	14	7.6
6	Massive pulmonary thromboembolism	12	6.5
7	CVA	11	6
8	Myocarditis	9	4.9
9	Peritonitis	7	3.8
10	Shock	6	3.2
11	Respiratory muscle fatigue	5	2.7
12	Diffuse intravascular coagulation (DIC)	5	2.7
13	Aneurysm	5	2.7
14	Acute pulmonary thromboembolism	4	2.2
15	Renal failure (ESRD)	3	1.6
16	Brain death	3	1.6
17	Cardiomegaly	2	1.1
18	Intracerebral hemorrhage (ICH)	1	0.55
19	Foreign body aspiration	1	0.55
20	Disseminated infection of the body	1	0.55
21	Seizure	1	0.55
22	Brain Tumor	1	0.55
23	Respiratory failure	1	0.55
24	Cardiomyopathy	1	0.55
25	Brain mass surgery	1	0.55
26	Metastasis	1	0.55
Total		**183**	**100**

Based on the findings of the present study, most important conditions affecting death were hypertension (8.2%), diabetes (6.0%), seizures (3.8%), and ischemic heart disease (2.2%). Also, in this study, it was found that 132 patients (72.1%) had underlying disease. 42 patients (22%) had a history of surgery and 55 (30.1%) had a history of drug use. Also, 59 patients (32.2%) had smoking and drugs, 21.3% had cigarette smoking, and 16.9% had opium use. The most important drugs used in these patients were metoral (7.1%), insulin (0.6%), losartan (5.5%), captopril (3.8%), chemotherapy drugs (3.8%), prednisolone (2.2%), and nitroglycerin (2.2%).

In examining the relationship between demographic factors and causes of death, it was identified that there was

no significant difference between men and women in the study population in the terminal cause of death. Only the number of deaths due to the terminal cause of acute respiratory distress syndrome in women (22.5%) was much higher than in men (7.1%) (P-value=0.041). There was no significant difference between men and women with COVID-19 death in the study regarding the presence of the first and second intermediate causes, the underlying cause, and the condition affecting death. There was no significant difference between single and married people in the study population in the terminal cause, first and second intermediating cause of death, and underlying cause of death. There was no significant difference in the terminal cause of death between urban and rural residents in the study population. Only the number of deaths due to the terminal cause of acute respiratory distress syndrome in rural residents (23.6%) was much higher than in urban residents (6.3%) (P-value=0.011). There was no significant difference between urban and rural residents in the study population about the existence of the first and second intermediate causes, the underlying cause, and the situation affecting death. Figure 2 shows the death map of COVID-19 patients based on the death certificate at BESAT Hospital.
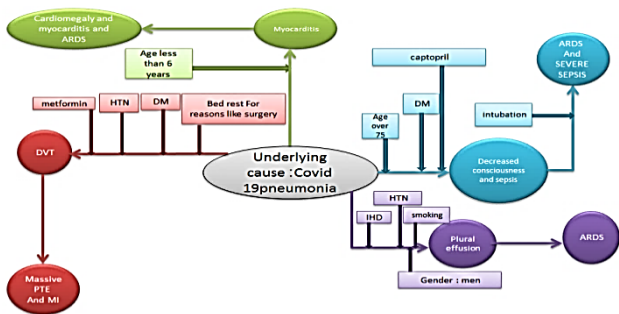

Figure 2. The death map of COVID-19 patients based on the death certificate at BESAT Hospital

The map is based on the death certificates and medical records of patients whose underlying cause of death was COVID-19 infection. Based on this map, 4 main pathways are obtained which cover a total of 60.7% of deaths due to the underlying cause of COVID-19.
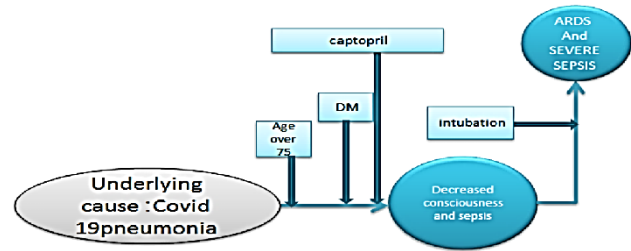

Figure 3. The first pathway of the death map of COVID-19 patients

According to the first pathway of the death map (Figure 3), whose prevalence was 20.3% of all deaths due to the underlying cause of COVID-19, following COVID-19, patients first suffered from loss of consciousness and sepsis and then required intubation during hospitalization; they eventually died of ARDS and severe sepsis. All the deaths surveyed in this pathway were over 75 years old, and 45% of them had diabetes; also, 52% of them had a history of taking ACEI (Angiotensin-converting enzyme inhibitors) drugs.
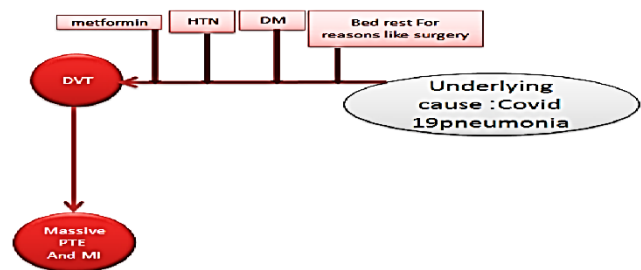

Figure 4. The second pathway of the death map of COVID-19 patients

According to the second pathway of the death map (Figure 4), whose prevalence was 27.3% of all deaths due to the underlying cause of COVID-19, patients with COVID-19 initially had vascular and coagulation problems such as DVT, and finally died due to massive PTE and MI. 20.1% of deaths from the pathway were due to bed rest for various reasons, 34% of them had diabetes and 86% of diabetics were treated with Metformin. 41% of them also had HTN.

According to the third pathway of the death map (Figure 5), the prevalence of which was 7.1% of all deaths due to the underlying cause of COVID-19, patients

following COVID-19 first developed myocarditis and eventually died of myocarditis and cardiomegaly. A small percentage of deaths on the pathway have been associated with ARDS. All deaths on the pathway were children under 6 years old.
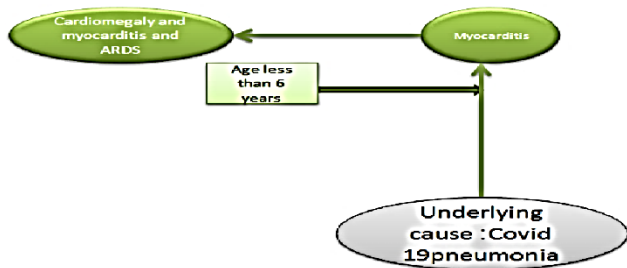

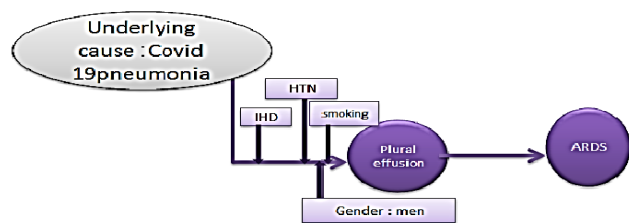**Figure 5.** The third pathway of the death map of COVID-19 patients

Figure 6. The fourth pathway of the death map of COVID-19 patients

According to the fourth pathway of the death map (Figure 6), which accounted for 6% of all deaths due to the underlying cause of COVID-19, patients with COVID-19 first developed pleural effusion, then ARDS, and eventually died. 65% of the deaths on this pathway were male and 22.5% of them had IHD and heart disease. 33% of deaths on the pathway had HTN and 27.5% of deaths had smoked.

DISCUSSION

This study aimed to draw a theoretical death map of these patients based on death certificates and medical records data. To achieve this goal, we investigated the medical records and the death certificates of patients with COVID-19 in BESAT hospital in Hamadan in 2020 to find out the underlying, intermediate, and terminal causes of death of these patients.

The demographic characteristics of the study population showed that the mean age of the study population was 56.1 years with a standard deviation of 22.1 years. The oldest was 96 years old and the youngest was 3 months old. 61.2% of the dead were male and 38.8% were female. Most of the dead were married (74.7%). Also, 60.6% of the dead lived in the urban and 39.4% in the rural area. Based on the analysis of demographic data of the research population, it was found that most married men living in the city and middle-aged and older individuals are at a higher risk of mortality. This group of society is compelled to work in high-risk environments due to the responsibility of meeting the economic needs of the family. Similar studies have reported the occurrence of death in old age. In 2020, Sun et al. conducted a retrospective study China and they showed that older age and lower lymphocyte count were associated with death in hospitalized patients with COVID-19, and careful monitoring and early intervention are needed to reduce mortality in these patients (13).

According to the results of our study, pneumonia, acute respiratory distress syndrome, severe sepsis, myocardial infarction, massive pulmonary thromboembolism, and cardiovascular accident (CVA) were the most important terminal causes of death in our COVID-19 patients. In other words, pulmonary problems and sepsis have been the leading causes of death in these patients. These findings are consistent with the findings of the studies conducted by Elsoukkary et al. and Elezkurtaj et al. (14,15). In a study by Elsoukkary et al., 94% of COVID-19-related deaths involved thromboembolism, and 88% had diffuse alveolar injury (14). The Elezkurtaj study findings, based on a review of COVID-19 patients' clinical history, indicated that septic shock, multiple organ failure, and respiratory failure were essential contributors to COVID-19 patient mortality. He stated that in most cases, respiratory failure was the main symptom while the most common clinical cause of death was sepsis due to infection (15). These findings indicate that COVID-19 infection can directly cause fatal lung damage. Death from bacterial

pulmonary infection and sepsis are common causes that can significantly endanger patients with severe COVID-19-associated lung injury.

In our study, acute respiratory distress syndrome (ARDS) had a statistically significant relationship with the death of COVID-19 patients. There was a significant relationship between ARDS (as a terminal cause of death), gender (more in women than in men), and place of residence (more in rural than in urban). Regarding other causes of death (first and second intermediate cause, underlying cause, and condition affecting death), there was no significant relationship with gender, marital status, and place of residence. In a similar study in Spain; pneumonia, ARDS, and diabetes mellitus were the variables that showed independent and statistically significant correlations with mortality (16) which was in line with our findings.

Results showed that 132 people (72.1%) had an underlying disease. 42 patients (22%) had a history of surgery, and 55 patients (30.1%) had a history of drug use. Also, 59 patients (32.2%) smoked and used opium, 21.3% of which smoked and 16.9% used opium. The underlying diseases that have played an important role in the death of the patients include hypertension (8.2%), diabetes (6.0%), seizure (3.8%), and ischemic heart disease (IHD) (2.2%). These findings are generally consistent with the findings of some studies conducted in other countries. For example, the findings of a study by Elezkurtaj et al., examining the clinical history of COVID-19 patients showed that diabetes, hypertension, and IHD were the main causes of COVID-19's progression to death (15). Also, based on the findings of other studies, it was found that diabetes, hypertension, renal failure, heart disease, and respiratory disorders were the most influential factors associated with death in patients with COVID-19 (17-27). A study conducted by Sepandi et al. showed that chronic diseases including type 2 diabetes, hypertension, renal impairment, respiratory disorders, and heart disease increase the risk of death in patients with COVID-19 (28). Identifying mortality-related factors in COVID-19 patients can help determine those at higher risk for death. Monitoring these factors can provide early warnings for interventions.

The death map is based on the death certificate of patients whose underlying cause of death was COVID-19. Based on the map, we can see that four main pathways account for a total of 60.6% of deaths attributed to COVID-19. The map indicates that the majority of patients passed away as a result of four main pathways, which began with COVID-19 and ultimately led to conditions such as sepsis, ARDS, myocarditis, MI, and PTE. Certain factors can increase the risk of deterioration and death, such as diabetes, being over 75 years old, taking ACE inhibitors (leading to death from sepsis and ARDS), smoking and high blood pressure, being male (in cases of pleural effusion and ARDS), being under 6 years old (in cases of myocarditis), having diabetes and hypertension, taking Metformin, and having a recent history of immobility (in cases of DVT, PTE, and MI).

Based on these results, health officials and healthcare providers should be able to identify and monitor patients with chronic diseases, including high blood pressure, and take effective measures to prevent them from contracting COVID-19. Physicians should also take important steps in offices, clinics, and hospitals, such as performing early echocardiography in children, providing respiratory support, and preventing deep vein thrombosis in adults during hospitalization. It is essential to inform the public through audio and video media, including radio and television. However, since the present study was performed at a single center, the results may not be applicable to all deceased patients with COVID-19. Therefore, similar multi-center studies can better identify the factors related to death in these patients.

CONCLUSION

The study's findings revealed that acute respiratory distress syndrome, severe sepsis, pneumonia, myocardial infarction, massive pulmonary thromboembolism, and CVA were the leading direct causes of death among

COVID-19 patients. Additionally, hypertension, diabetes, seizures, and ischemic heart disease significantly contributed to the mortality of these patients. Based on the data, it was observed that most patients followed four main paths, starting with COVID-19 and ultimately succumbing to conditions such as sepsis, ARDS, myocarditis, MI, and PTE. Certain factors, such as diabetes and age over 75 years, ACEI (leading to death due to sepsis and ARDS), smoking, hypertension, and male gender (resulting in pleural effusion and ARDS), and age under 6 years (associated with myocarditis), as well as diabetes, hypertension, Metformin use, and recent inactivity (impacting DVT, PTE, and MI), made individuals more susceptible to disease progression and death. Consequently, it is recommended to monitor patients with chronic conditions like hypertension and diabetes, and for physicians to consider measures such as early echocardiography in children, respiratory support, and venous thrombosis prevention in adults admitted to the hospital.

Acknowledgments

Conflict of interest

There is no conflict of interest to be declared.

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