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COVID19 MORTALITY CORRELATION WITH THE BLOOD AND CYTOKINE LEVELS PARAMETERS IN 2021

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Abstract
The COVID-19 epidemic has strained healthcare systems globally. Effective patient care and public health policies need understanding COVID-19 mortality variables. This research examines how demographics, comorbidities, cytokine parameters, and hospitalization time affect COVID-19 mortality. The research retrospectively examined 100 Iraqi COVID-19 patients in 2021. Data from Medical City Hospital and Al-Kadhimiya Hospital were analyzed using SPSS and Excel. Study participants were of various ages and genders. The 2021 COVID-19 death rate was 22%, depending on age, gender, and comorbidities. Out of persons aged ≤30 (n=9), 22.2% died from the illness. In the 31-40 age range (n=24), 25.0% died. The 41-50 age group (n=15) had a 40.0% death rate. In the 51-60 age range (n=27), 25.9% died. The 61-70 age group (n=18) had a 5.6% death rate. No one over 70 (n=7) died. The age of patients, but not gender, are significantly associated with mortality. Among the parameters analyzed, ferritin, D-dimer, lymphocytes, and the neutrophil-to-lymphocyte ratio (NLR) levels showed significant differences between the deceased and alive groups (p-value <0.05). Comorbidity analysis demonstrated that cardiovascular diseases, malignancy, kidney diseases, and bacterial infections were significantly associated with higher mortality rates in COVID-19 patients, while liver disease, diabetes mellitus (DM), and hypertension (HT) did not show significant associations. IL6, IL10, and IL12 cytokines levels differed significantly between died and surviving patients. Elevated levels of these interleukins were associated with increased mortality risk, while TNF-a levels showed no significant difference.

Keywords COVID-19, Mortality, Cytokines, comorbidities, 2021.

INTRODUCTION

The COVID-19 pandemic is the current source of concern for the entire world. The best course of action in this case is suggested to remain socially aloof and to maintain awareness of the circumstances (World Health Organization, 2022a).

The Coronavirus Disease 2019 (COVID-19) pandemic has brought to light the difficulties faced by the healthcare system in Iraq. This system has a limited number of beds in intensive care units, as

well as medical personnel and equipment, which contributes to high infection rates and death (Malaeb et al., 2023).

On February 24, 2020, an Iranian student who had been to Iraq was diagnosed as the country's first case of COVID-19. On May 24, 2020, there were 4469 confirmed COVID-19 infections, 160 fatalities, and 2738 individuals who had recovered from the virus. To stop the disease from spreading across the country, the authorities have put in place significant public health efforts. However, the number of instances is still sharply increasing (Sarhan et al., 2020). In that direction, as soon as the first case was discovered, the Iraqi government and the regional government of Kurdistan began adopting a variety of measures. They have continued to adjust and expand their scope in response to the virus's spread pattern, giving the protection of citizens' lives and safety top priority. The government is aware that the implemented measures (such as curfews, mobility restrictions, the associated confinement of businesses outside of those deemed necessary, and the closing of schools and universities) would have detrimental socioeconomic effects on the population and their living conditions (UNICEF, 2020).

While immunological responses were effectively developed to stop viral replication in moderate instances, severe cases resulted in viral sepsis with immunologic impairment due to uncontrolled inflammation and microcirculation dysfunctions (Li et al., 2020). Immunological dysfunction was linked to the severity of the illness. SARS-CoV-2, in particular in some life-threatening cases, might cause catastrophic immune system damage that, at its worst, would end in death (Tong et al., 2021).

In Iraq, from 3 January 2020 to 5:28pm CET, 7 December 2022, there have been 2,463,296 confirmed cases of COVID-19 with 25,363 deaths, reported to WHO. As of 28 November 2022, a total of 19,507,805 vaccine doses have been administered (World Health Organization, 2022b)

Through a particular CRP receptor, CRP can improve phagocyte phagocytosis and eliminate a variety of harmful bacteria. A cytokine reaction storm (CRS) that can be set off during COVID-19 pneumonia is linked to a significant death rate for the virus (Azar et al., 2020). Hepatocytes are stimulated by cytokines like IL-6 and TNF-a to generate CRP (Luan et al., 2021). The biomarker CRP is highly higher in the early stages of inflammation and most strongly associated with COVID-19 development (Ponti et al., 2020; Chan et al., 2020), and also before any warning signs of crucial computerized tomography (CT) scan results. Acute-phase proteins including CRP, procalcitonin (PCT), and IL-6 revealed a rising tendency in non-survivors but a constant or declining trend in survivors in a number of retrospective comparative studies comparing the two groups (Chen et al., 2020).

Research that was conducted in Iraq by Mawlood & Lafta, (2022), found that the trend of COVID-19 in Iraq exhibited two peaks: one in the months of August-October 2020 and one in the months of March-July 2021. The study also found that males were more likely to experience morbidity, mortality, and fatality than females.

Iran and Iraq are two nations that are adjoining one another, and despite the fact that the sickness is currently impacting almost every country, a significant variance in the number of fatalities has drawn our notice. However, if one investigates the fatalities that have been recorded, one finds that the number of deaths per one million people (1MP) in Iraq is much lower than that of Iran (i.e., 601 vs. 1642) (Amani et al., 2022).

2. MATERIAL AND METHODS

2.1 Study design: a retrospective study was conducted on 100 patients with Covid-19 for the year 2021 in Iraq hospitals. This study took place in Baghdad province, serving as a representative sample for Iraq. The research was conducted at Medical City Hospital and Al-Kadhimiya Hospital, with an equal distribution of samples between the two hospitals. The data obtained from hospital records included information about demographic characteristics, pre-existing comorbidities, and immunological parameters.

2.2 Criteria for Inclusion and Exclusion:

1. Inclusion criteria: This study included individuals of all ages and both sexes. The patients' group consisted of individuals who had been diagnosed with severe acute respiratory syndrome caused by SARS-COV2, in the past, and had been admitted to the hospital.

2. Exclusion criteria: The study excluded individuals who tested negative for SARSCOV2 by RT-PCR. Patients with a confirmed immunological disorder, specifically autoimmune disease, were excluded. Individuals who were receiving long-term steroid or immune-modulating treatment were excluded in the patient groups.

2.3: Measurement of cytokine levels using an ELISA kit

In this study, hospitals measured the cytokine level of COVID-19 during the acute phase and in the morning. ELISA kits designed to detect specific cytokines, including IL-6, IL-10, IL-12, and TNF-a, were employed in this study. To establish a reference, standard curves were constructed using known concentrations of the respective cytokine standards. Serum or plasma samples, suitably diluted, were introduced into ELISA plates coated with antibodies specifically targeting these cytokines. Following a period of incubation and subsequent washing steps, enzyme-conjugated secondary antibodies were introduced. A substrate solution was then added to initiate a color reaction, which was subsequently quantified through spectrophotometric measurements. The concentrations of the cytokines were determined by comparing the optical density values obtained from the samples with the standard curve, allowing for precise quantification.

Cytokines IL-6, IL-10, IL-12, and TNF-a regulate the immune response, making them important in COVID-19. In severe COVID-19 instances, IL-6, an inflammatory marker, is high. IL-10, an anti-inflammatory cytokine, controls overactive immune responses. IL-12 activates natural killer and T cells, which combat viral infections. TNF-a and the inflammatory response can cause cytokine storms in severe COVID-19 instances. Despite their function in the immune response, these cytokines are closely evaluated in COVID-19 patients because to their influence on disease severity and progression. Clinicians can measure immune response and modify treatment by monitoring their levels.

2.4 Measurement of biological parameters

In the study hospitals, The AFIAS assay was designed to measure D-Dimer and ferritin levels. While The measurements included five parameters to determine the counts and percentages of white blood cells. in the study, hospitals obtained Whole blood from an EDTA tube and analyzed using an automated hematology analyzer from Sysmex Corp., Japan. The parameters measured were total WBCs, Lymphocytes, Neutrophils, and platelets.

2.5 Statistical Analysis: The data collected in this study underwent comprehensive analysis and presentation, utilizing statistical tools such as the Statistical Package for the Social Sciences (SPSS) version 28 and Microsoft Office Excel 2010. Numeric data were summarized by calculating the mean, standard deviation, and range, following the assessment of normality using the Kolmogorov-Smirnov normality test to ascertain whether the variables adhered to a normal distribution. To assess differences in means between two groups, an independent sample test was applied. Additionally, for comparisons involving three or more groups, assuming that the variable met the parametric assumptions Furthermore, categorical variables were assessed using the Chi-square test to explore potential relationships between pairs of categorical variables. To measure risk, odds ratios along with 95% confidence intervals were calculated. Operator Characteristic (ROC) curve analysis was utilized to identify the most suitable cutoff values, and sensitivity and specificity analyses were carried out accordingly. The significance level for all analyses was set at a P-value of 0.05 or lower, with a highly significant threshold at 0.01 or lower. This thorough statistical technique assures the study's robustness and reliability and supports the data analysis's results (Daniel and Cross, 2018).

3. Results and Discussion

Table (3.1) details the study sample's demographics, including age and gender distribution. The age distribution is wide, with 9% under 30, 24% 31-40, 15% 41-50, 27% 51-60, 18% 61-70, and 7% beyond 70. With 54% male and 46% female, gender distribution is about equal.

Table (3.1): The distribution of the study's population samples based on the demographic characteristics of the participants

Demographic Characteristics		No.	Percent
Age groups	≤30 year	9	9.0
	31-40 year	24	24.0
	41-50 year	15	15.0
	51-60 year	27	27.0
	61-70 year	18	18.0
	>70 years	7	7.0
Gender	Male	54	54.0
	Female	46	46.0

The study found that 22.0% of COVID-19 patients died and 78.0% recovered. Table 3.2 shows that 22.2% of those aged ≤30 (n=9) died from the disease, while 77.8% survived. In the 31-40 age group (n=24), 25% died and 75% survived. In the 41-50 age range (n=15), 40.0% died and 60.0% survived. In the 51-60 age group (n=27), 25.9% died and 74.1% survived. The 61-70 age group (n=18) reported 5.6% mortality and 94.4% survival. Everyone over 70 survived (n=7). The Chi-squared score of 8.012 and p-value of 0.156 indicate that age groups do not significantly affect COVID-19 mortality. This implies that age does not predict death in COVID-19 patients in this group. Gender's Chi-squared is 2.284 and p-value 0.131. This dataset similarly reveals no statistical significance for gender or mortality. These results agreed with the study findings done by Richardson et al., (2020), which reported an overall in-hospital mortality rate of 21%. However, the mortality rate varied significantly among different age groups, with rates of 3% for patients under 30 years old and over 50% for patients aged 80 years and older. Also, a study by Ioannidis, (2021), which found that 23% of individuals infected with COVID-19 would die from the disease. However, we can discuss several general factors have been associated with COVID-19 mortality.

Table (3.2): Relationship between the Deceased and Surviving Groups in the Context of Demographic Characteristics in COVID-19 Cases.

		Mortality				X^2	P. value
		Died		Non-died			
		No.	%	No.	%		
Age groups	≤30 year (n=9)	2	22.2	7	77.8	8.012	0.156
	31-40 year (n=24)	6	25.0	18	75.0		
	41-50 year (n=15)	6	40.0	9	60.0		
	51-60 year (n=27)	7	25.9	20	74.1		
	61-70 year (n=18)	1	5.6	17	94.4		
	>70 years (n=7)	0	0.0	7	100		
Gender	Male	15	27.8	39	72.2	2.284	0.131
	Female	7	15.2	39	84.8		

COVID-19 hospital stays and deaths in 2021 are shown in Table 3.3. From non-admitted to various hospitalization durations, the data is grouped. More COVID-19 patients died after 14 days in the hospital, highlighting the need for prolonged therapy. These patients died more than non-admitted ones (p=0.020; OR (95% C.I) = 14.22 (1.52-132.73)). Shorter hospital stays of 5-9 or 10-14 days did not influence mortality. These results are consistent with the study findings done by Grasselli et al., (2020) , which reported that patients with severe respiratory symptoms may require various forms of respiratory support, such as high-flow nasal cannula, non-invasive ventilation (e.g., CPAP), or invasive mechanical ventilation. The need for prolonged respiratory support can extend the hospital stay and is associated with increased mortality risk.

Table (3.3): Association between the number of days of hospital stay and mortality in patients with COVID-19 in the year 2021

		Died		Non-died		B	P. value	OR (95% C.I)
		No	%	No.	%			
Number of days of hospital stay in 2021	Non-admitted (n=17)	1	5.9	16	94.1	Reference		
	<5 days (n=20)	2	10.0	18	90.0	0.575	0.651	1.778 (0.147-21.509)
	5-9 days (n=30)	7	23.3	23	76.7	1.583	0.157	4.870 (0.545-43.523)

	10-14 days (n=16)	4	25.0	12	75.0	1.674	0.157	5.333 (0.526-54.032)
	>14 days (n=17)	8	47.1	9	52.9	2.655	**0.020**	**14.222 (1.524-132.730)**

Table (4.11) compares laboratory values of died and surviving Covid-19 patients in 2021.

Significant changes in ferritin, D-dimer, lymphocytes, and neutrophil-to-lymphocyte ratio (NLR) levels were observed between died and living groups, as demonstrated by p-value (<0.05). However, platelet count, CRP, neutrophil, and white blood cells did not change significantly.

Regarding ferritin levels, the mean value for the deceased group was 736.591 ng/mL, while for the alive group, it was 494.673 ng/mL. The standard deviation was higher in the deceased group (567.3619 ng/mL) compared to the alive group (375.0624 ng/mL). The t-test value was 2.365, indicating a statistically significant difference between the two groups, as supported by the p-value of 0.020. This suggests that ferritin levels may be associated with the outcome of Covid-19 patients, with higher levels potentially being linked to death. Findings from a study done by Ahmed et al., (2021), agree with results of this study and reported that higher ferritin levels associated with the mortality of Covid-19 patients . While these results disagreed with Feld et al., (2020), which reported that ferritin levels in patients with COVID-19 were a poor predictor of mortality. There was a significant association between D-dimer levels and groups, p value < 0.05. For D-dimer levels, the mean +SD value for the dead group was 1386.2153+990.06946 ng/mL, and for the alive group, it was 898.6377+679.97126 ng/mL. In Covid-19 patients, increased D-dimer levels may increase mortality. These results consistent with the previous studies (Tang et al., 2020 ;Yao et al., 2020; Zhou et al., 2020) which found that higher D-dimer levels have been associated with an increased risk of mortality in COVID-19 patients. D-dimer is a fibrin degradation product that is produced when blood clots are broken down. In severe cases of COVID-19, abnormal blood clotting and disseminated intravascular coagulation (DIC) can occur, leading to complications and increased mortality. This study found a strong correlation between lymphocyte counts and group values (p < 0.05). In terms of lymphocyte counts, the dead group had a mean+ SD of 23.5005+ 11.71203 cells/µL, whereas the living group had 31.2176+ 12.05188 cells/µL. A statistically significant difference was found in the t-test value of 2.668 and p-value of 0.009. In Covid-19 patients, reduced lymphocyte counts may increase mortality. These results are consistent with Henry et al., (2020), which revealed that lymphopenia associated with an increased risk of mortality in Covid-19 patients. Also, a study by Zhang et al., (2021), who revealed that lymphocyte blood levels that remain low can predict the death of patients with COVID-19. We can discuss that lymphocytes are not only involved in antiviral defense but also in maintaining tissue homeostasis and repair. Lymphopenia can impair tissue repair mechanisms and increase the vulnerability of organs to damage caused by the virus or the immune response itself. Organ dysfunction or failure can significantly contribute to mortality in COVID-19 patients. The study found a strong correlation between neutrophil-to-lymphocyte ratio and groups (p < 0.05). The dead and living groups had different neutrophil-to-lymphocyte ratios (NLRs). The deceased group had a mean +SD NLR of 3.9915+ 2.63393, whereas the alive group had 2.7847+ 1.84088. Covid-19 patients with a higher NLR may have lower outcomes. This supported Liu et al., (2020) observation that Covid-19 patients with greater NLRs had higher death rates. A greater NLR in COVID-19 patients may predict disease severity and death. It indicates the

patient's immunological state and virus-fighting capabilities. Platelet count, CRP, neutrophils, and white blood cells did not significantly affect Covid-19 mortality in this trial. Platelet count, CRP levels, neutrophil count, and white blood cell count are part of the immune response and inflammation, but not the full illness process. COVID-19 is complicated by age, comorbidities, immunological response, and viral load.

Table (4.11): Differences in Laboratory Parameters between Deceased and Surviving Patients with Covid-19 (for year 2021)

	Groups	Mean	SD	SE	t. test	*P. value*
WBCs	Died	8.9350	3.31045	0.70579	0.331	0.741
	Alive	9.2258	3.72306	0.42155		
Ferritin	Died	736.591	567.3619	120.9620	2.365	**0.020**
	Alive	494.673	375.0624	42.4674		
Platelets	Died	258.273	89.0972	18.9956	1.142	0.256
	Alive	230.201	104.9833	11.8870		
D-Dimer	Died	1386.2153	990.06946	112.10329	2.166	**0.033**
	Alive	898.6377	679.97126	144.97036		
CRP	Died	33.0045	20.52440	4.37582	0.862	0.391
	Alive	38.2651	26.42078	2.99156		
Lymphocytes	Died	23.5005	11.71203	2.49701	2.668	**0.009**
	Alive	31.2176	12.05188	1.36461		
Neutrophil	Died	69.5095	15.09551	3.21837	0.145	0.885
	Alive	68.9888	14.86238	1.68283		
NLR	Died	3.9915	2.63393	0.56156	2.454	**0.016**
	Alive	2.7847	1.84088	0.20844		

Table (3.10) shows COVID-19 mortality-related comorbidities in 2021. There were 7 fatalities (31.8%) among cardiovascular disease patients compared to 9 deaths (11.5%) among those without the condition (p-value = 0.022; OR= 3.578, 95% C.I. (1.15 to 11.12)). Patients with malignancy had 4 deaths (18.2%) compared to 1 death (1.3%) in those without malignancy (p-value = 0.001; OR =17.11, 95% C.I. (1.80 to 162.44)). Also, renal problems are associated with death. There was a significant connection between renal disease and mortality, with 3 (13.6%) and 1 (1.3%), respectively (p-value = 0.009; OR = 12.15, 95% C.I. 1.19 to 123.49). Patients with bacterial infections had a greater mortality rate, with 19 deaths (86.4%) compared to 38 deaths (48.7%) among those without them (p-value is 0.002, OR=6.66, 95% C.I. (1.82 to 24.36)). 2 (9.1%) of liver disease patients died, compared to 1 (1.3%) of those without it. The p-value of 0.058 implies significance, however it does not meet the OR=7.70 criteria, with a 95% C.I. of 0.66 to 89.26. Diabetes mellitus (DM) and hypertension (HT) have no significant connection with mortality in the research (p > 0.05). These findings agreed with the recent studies (Biswas et al., 2021; Tian et al., 2020), Cao et al., 2020; Huang et al., 2020; Guan et al., 2019; Muniyappa & Gubbi, 2020). From these results, we can summarize possible causes of death

for patients with CVD and Covid including; 1) Patients with CVD may be more susceptible to ARDS due to pre-existing lung damage or reduced lung function (Matthay et al., 2019). 2) COVID-19 can increase the risk of blood clots, which can lead to heart attack, stroke, or pulmonary embolism in patients with CVD (Merschel, 2022).

Table (3.10): Assessing the comorbidity events associated with mortality in patients with COVID-19 in the year 2021

		Died		A live		P. value	OR (95% C.I)
		No.	Percent	No.	Percent		
Cardiovascular diseases	Yes	7	31.8%	9	11.5%	**0.022**	**3.578 (1.150-11.127**
	No	15	68.2%	69	88.5%		
Malignancy	Yes	4	18.2%	1	1.3%	**0.001**	**17.111 (1.802-162.440)**
	No	18	81.8%	77	98.7%		
Liver disease	Yes	2	9.1%	1	1.3%	0.058	7.700 (0.664-89.260)
	No	20	90.9%	77	98.7%		
Kidney diseases	Yes	3	13.6%	1	1.3%	**0.009**	**12.158 (1.197-123.491)**
	No	19	86.4%	77	98.7%		
Bacterial infections	Yes	19	86.4%	38	48.7%	**0.002**	**6.667 (1.824-24.366)**
	No	3	13.6%	40	51.3%		
diabetes mellitus (DM)	Yes	12	54.5%	44	56.4%	0.876	-
	No	10	45.5%	34	43.6%		
Hypertension (HT)	Yes	14	63.6%	44	56.4%	0.544	-
	No	8	36.4%	34	43.6%		

This study found substantial differences in IL6, IL10, and IL12 levels between died and surviving persons in table 3.4. The study revealed that people who did not survive had considerably greater levels of these interleukins ($P < 0.05$). There were no significant TNF-a changes between died and surviving individuals ($P > 0.05$). The present results are correspond to the study findings done by Aziz et al., (2020) and Herold et al., (2020b), which found that IL-6 and IL-10 have been proposed as potential biomarkers for predicting disease severity and mortality in COVID-19 patients. High levels of IL-6 and IL-10 have been found to correlate with worse clinical outcomes and increased mortality rates. A study by Kox et al., (2020) reported that COVID-19 can trigger an excessive immune response, leading to a cytokine storm characterized by elevated levels of pro-inflammatory cytokines like IL-6 and IL-12. This dysregulated immune response can contribute to tissue damage, organ dysfunction, and an increased risk of mortality.

Table (3.4) comparison between mean of died and a live individual infected with SARSCOV2 according to cytokines levels

		N	Mean	SD	T. test	P. value
TNF-a	Died	22	11.283	1.7268	0.488	0.626
	A live	78	11.080	1.7144		
IL6	Died	22	8.461	0.8795	2.188	**0.031**
	A live	78	7.983	0.9107		
IL10	Died	22	207.327	26.0018	2.289	**0.024**
	A live	78	191.165	30.0741		
IL12	Died	22	8.644	0.8433	3.896	**<0.001**
	A live	78	7.809	0.8982		

In table (3.5), the results reveal that the age range "31-40 years," IL6 is associated with decreased likelihood of COVID-19 severity (OR = 0.297, p-value 0.032). In the "41-50 years" age group, IL6 follows a similar trend (OR = 0.285, p = 0.035). Higher IL10 levels for the age range "51-60 years" are linked to greater COVID-19 severity (OR = 1.058, p < 0.001). Compared to "61-70 years" and ">70 years," cytokines and COVID-19 results are not statistically significant, with p-values over 0.05. This data shows that age and cytokine responses have a multifaceted role in illness severity in COVID-19 patients.

Table (3.5): The relationship between cytokine levels parameters of the patients with Covid-19 and age groups

Age groups		B	P. value	OR	95% Confidence Interval for OR	
					Lower Bound	Upper Bound
31-40 year	Intercept	2.725	0.599			
	IL6	-1.216	0.032	0.297	0.098	0.899
	IL10	0.032	0.055	1.032	0.999	1.066
	IL12	0.300	0.516	1.350	0.546	3.337
41-50 year	Intercept	3.132	0.570			
	IL6	-1.254	0.035	0.285	0.089	0.915
	IL10	0.029	0.103	1.029	0.994	1.065
	IL12	0.301	0.545	1.351	0.510	3.577
51-60 year	Intercept	-0.953	0.856			
	IL6	-1.097	0.057	0.334	0.108	1.031
	IL10	0.056	0.001	1.058	1.023	1.095

	IL12	0.034	0.942	1.034	0.417	2.567
61-70 year	Intercept	1.572	0.771			
	IL6	-0.633	0.277	0.531	0.170	1.663
	IL10	0.030	0.072	1.030	0.997	1.065
	IL12	-0.143	0.762	0.867	0.343	2.191
>70 years	Intercept	1.592	0.804			
	IL6	-0.615	0.364	0.540	0.143	2.038
	IL10	0.008	0.694	1.008	0.969	1.049
	IL12	0.236	0.678	1.266	0.417	3.845

The reference category is: ≤30 year. (Multinominal logistic regression analysis)

Table 3.6 shows that male cytokine levels were not significantly different from females, as shown by the p-values >0.05, for all cytokines (IL6, IL10, and IL12). Supporting the lack of a gender-cytokine connection in our study. In this dataset, gender does not seem to be a key factor in COVID-19 patient cytokine levels.

Table (3.6): The relationship between cytokine levels parameters of the patients with Covid-19 and gender

Gender		B	P. value	OR	95% Confidence Interval for Exp(B)	
					Lower Bound	Upper Bound
Male	Intercept	1.345	0.564			
	IL6	-0.073	0.755	0.930	0.588	1.469
	IL10	0.005	0.471	1.005	0.991	1.020
	IL12	-0.205	0.362	0.815	0.524	1.266

The reference category is: Female. (Multinominal logistic regression analysis)

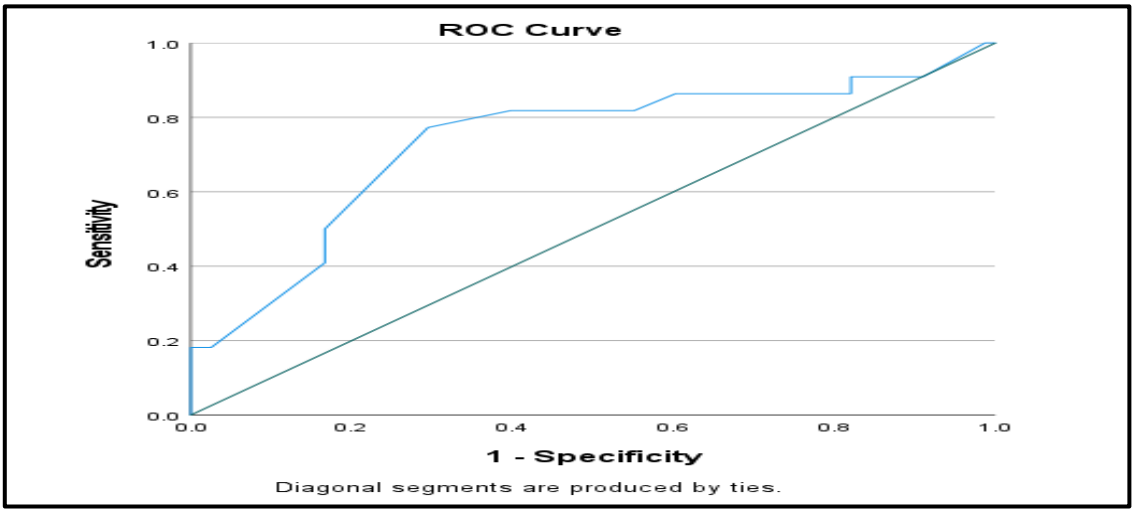

Figure (3.3) Receiver operator characteristic curve analysis used to determine the potential diagnostic cutoff value for IL6

To assess the IL6 cutoff value and predict mortality using diagnostic tests, we conducted receiver operator characteristic (ROC) curve analysis. The corresponding results are presented in the following table (3.7) and figure (3.3). The determined IL6 cutoff value was greater than 8.66. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve, and p-value were 77.3%, 70.5%, 42.5%, 91.7%, 0.735 (0.604-0.865), and 0.001, respectively.

Table (3.7): Sensitivity and specificity of IL6 level in death from SARS-COV2

IL6 level (fold)	**Died NO. = 22**	**A live NO. = 78**
Predictive- Died > 8.66	17 (77.3%)	23 (29.5%)
Predictive-A live ≤ 8.66	5 (22.7%)	55 (70.5%)
Sensitivity %	77.3 %	
Specificity %	70.5 %	
PPV %	42.5 %	
NPV %	91.7 %	
AUC (95% CI)	0.735 (0.604- 0.865)	
P. value	0.001*	

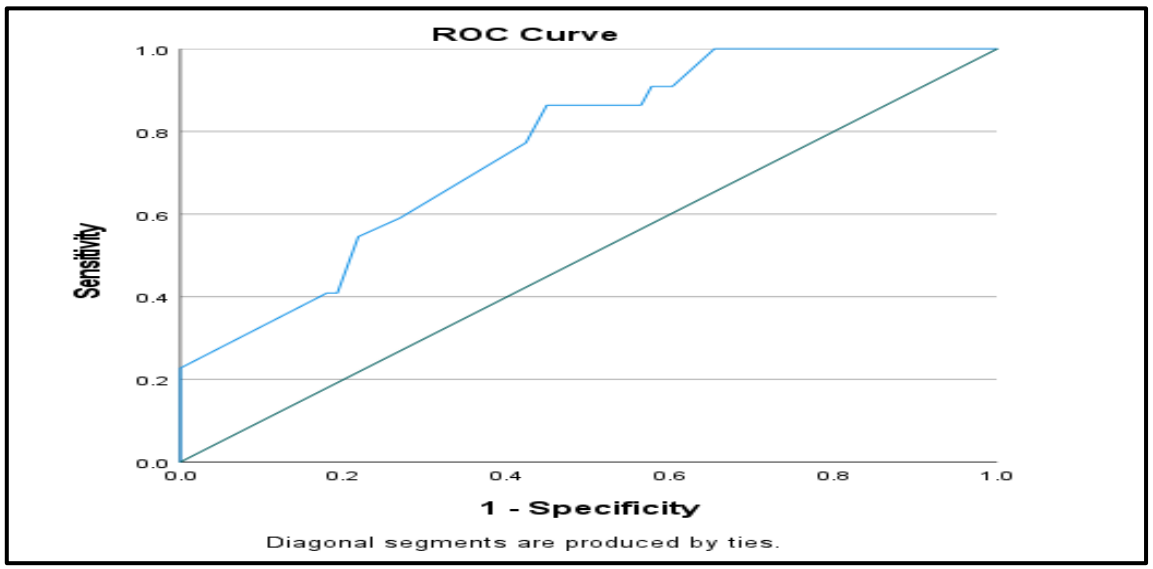

Figure (3.4) Receiver operator characteristic curve analysis used to determine the potential diagnostic cutoff value for IL10

To assess the IL10 cutoff value and predict mortality using diagnostic tests, we conducted receiver operator characteristic (ROC) curve analysis. The corresponding results are presented in the following table (3.8) and figure (3.4). The determined IL10 cutoff value was greater than 195. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve, and p-value were 86.4%, 55.1%, 35.2%, 93.5%, 0.759 (0.655-0.863), and <0.001, respectively.

Table (3.8): Sensitivity and specificity of IL10 level in death from SARS-COV2

IL10 level (fold)	Died NO. = 22	A live NO. = 78
Predictive- Died > 195	19 (86.4%)	35 (44.9%)
Predictive- A live ≤ 195	3 (13.6%)	43 (55.1%)
Sensitivity %	86.4 %	
Specificity %	55.1 %	
PPV %	35.2 %	
NPV %	93.5 %	
AUC (95% CI)	0.759(0.655- 0.863)	
P. value	<0.001*	

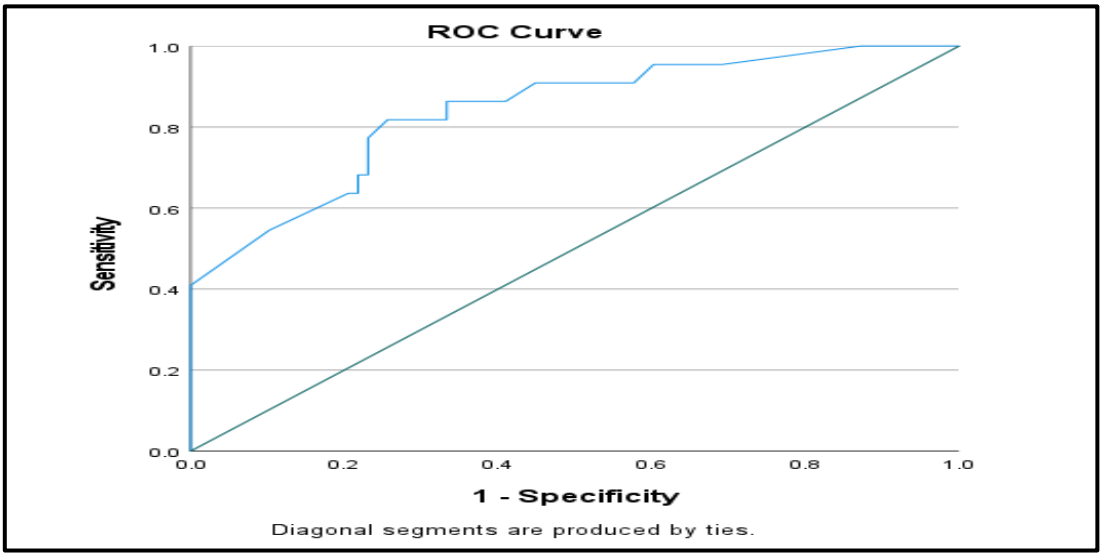

Figure (3.5) Receiver operator characteristic curve analysis used to determine the potential diagnostic cutoff value for IL12

To assess the IL12 cutoff value and predict mortality using diagnostic tests, we conducted receiver operator characteristic (ROC) curve analysis. The corresponding results are presented in the following table (3.9) and figure (3.5). The determined IL12 cutoff value was greater than 7.91. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the curve, and p-value were 86.4%, 64.1%, 40.4%, 94.3%, 0.840 (0.744-0.936), and <0.001, respectively.

Table (3.9): Sensitivity and specificity of IL12 level in death from SARS-COV2

IL12 level (fold)	Died NO. = 22	A live NO. = 78
Predictive- Died > 7.91	19 (86.4%)	28 (35.9%)
Predictive- A live ≤ 7.91	3 (13.6%)	50 (64.1%)
Sensitivity %	86.4 %	
Specificity %	64.1 %	
PPV %	40.4 %	
NPV %	94.3 %	
AUC (95% CI)	0.840(0.744- 0.936)	

P. value	<0.001*

CONCLUSIONS

Elevated IL6, IL10, and IL12 levels increased mortality, however TNF-a did not. These data suggest cytokines may be COVID-19 disease severity and mortality biomarkers. Cardiovascular disease, cancer, liver disease, renal disease, and bacterial infections elevated mortality risk. The outcomes of this study improve COVID-19 understanding and can improve patient care, risk assessment, and public health activities in Iraq and internationally. The minimal number of patients limits this investigation. These findings need to be validated with bigger samples.

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