

COVID-19 in Patients with Different Hematological Malignancies: Treatment Strategy and Outcome: An Iraqi Experience

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Abstract

Background: Patients with hematological malignancies may have higher rates of morbidity and mortality due to SARS-COVID-19 than those in the general population. **Objectives:** To evaluate the outcome of SARS-COVID-19 in patients with different hematological malignancies undergoing active or modified therapy. **Settings:** This was a retrospective cohort, multicenter study conducted on 167 patients diagnosed with SARS-COVID-19. The selected patients had been diagnosed with different hematological malignancies and had received treatment (chemotherapy or immunosuppression). The study was carried out in different centers across Iraq between 1 December 2020 and 1 December 2021. **Patients and Methods:** This study was conducted at seven hematology centers across Iraq with 167 patients; of these, this study enrolled 88 (52.7%) males and 79 (47.3%) females (mean age 51.9 ± 18.3 years). All patients had had a COVID-19 infection confirmed through the amplification of RNA-specific fragments by real-time reverse transcriptase polymerase chain reaction (RT-PCR) of the nasopharyngeal swab specimens, and by computed tomography (CT) of the chest. Demographic data were obtained from patient files, which included the type of hematological malignancy, treatment (chemotherapy, immunotherapy, supportive), severity of COVID-19, modification of treatment, and disease outcome for patients, whether alive or not. Patients identified as having benign or non-hematological malignancies were excluded. **Results:** The treatment protocol was modified in 124 patients (74.3%), while 43 patients (25.7%) continued on the same protocol. Regarding treatment outcomes, 77.2% of patients were alive at the end of the study, and 22.8% had died. The survival of COVID-19 patients did not change significantly when the treatment protocol was modified compared to those who continued on treatment as per protocol. The death rate was significantly higher among patients with severe disease compared to those with mild and moderate disease (61.4% vs. 0% and 5.0%, respectively) ($p < 0.001$). **Conclusions:** The management of patients with hematological malignancies during the COVID-19 pandemic may be challenging, with higher mortality in patients with concurrent hematological malignancies and COVID-19. The survival of COVID-19 patients did not change significantly when treatment was modified. Age groups, sex, type of hematological malignancy, and disease status did not affect the survival of these patients. The death rate was significantly higher among patients with hematological malignancies and severe COVID-19 compared with mild or moderate disease.

Keywords: COVID-19, hematological malignancies, outcomes

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INTRODUCTION

The coronavirus pandemic, SARS-CoV-2, is known to cause severe infection (COVID-19) in patients with comorbidities, particularly cancer or those in an immunosuppressed state. Moreover, patients with cancer are often admitted for treatment and monitoring, and so they may be at risk of getting COVID-19 [1, 2]. Results from New York demonstrate that mortality during the COVID-19 pandemic was higher in patients with cancer, especially hematological malignancies, than in other patients. Nevertheless, these estimates are controversial, and it is unclear if they apply to patients with hematologic malignancies [3, 4].

In a recent meta-analysis, the prevalence of COVID-19 in cancer patients was found to be 2% [5]. Overall case fatality rates have been reported as 1–5% in COVID-19 patients than in the general population, and potentially >30% in patients with cancer; thus, careful consideration should be given to the risk of COVID-19 in leukemia [6].

A retrospective study from three centers in China showed a mortality rate of 28.6% in patients with cancer, and patients who had received antitumor therapy within 14 days prior to infection had a higher risk of severe infection [7]. Extra caution is therefore warranted when dealing with patients suffering from hematological malignancies, as they will be more vulnerable to the direct and indirect risks of COVID-19 [8].

Another challenging issue is the timely administration of treatment protocols for hematological malignancy and, at the same time, the prevention and management of the infection, taking into consideration that the guidelines for the management of hematologic patients in the current SARS-CoV-2 outbreak are not evidence-based [9–11]. Up to now, there is scarce evidence to guide therapeutic decisions for the care of hematology patients during the pandemic, and, therefore, decision-making is likely to be challenging. Given the extraordinary amount of rapidly evolving data and recommendations, it may be impossible for clinicians to stay abreast of all the information [12, 13].

The European Society of Medical Oncology (ESMO) guidelines classify interventions based on disease status and are easy to use, with the priority levels for different hematological interventions being divided into high, intermediate, and low [14]. Based on this information, this study was designed to evaluate the outcome of SARS-COVID-19 in patients with different hematological malignancies undergoing active or modified therapy.

PATIENTS AND METHODS

A retrospective, multicenter, cohort study included 167 adult patients with different hematological malignancies who were receiving treatment (chemotherapy, immunosuppression, or supportive therapy). Data were collected from seven hematology centers across Iraq from 1 December 2020 to 1 December 2021. Patients were stratified according to the underlying hematologic malignancy, gender, and age (<30 years, 31–50, 51–65, and >65 years) as well as COVID-19 risk status.

All adult patients were diagnosed with COVID-19, confirmed by the detection of COVID-19 RNA-specific fragments by real-time reverse transcriptase polymerase chain reaction (RT-PCR) of the nasopharyngeal swab specimens, and by CT of the chest; they were stratified as either positive or negative. The study included all adult patients admitted to the hospital or who had consulted the outpatient clinic with a diagnosis of COVID-19 and hematological malignancies; these patients were then classified according to treatment response, whether this was complete or partial remission, or relapse. Regarding the severity of COVID-19, the patients were also classified as mild, moderate, or severe, according to the WHO COVID-19 Case Definition, which was updated on 7 August 2020 [15].

The outcome for COVID-19 was assigned either as alive or dead, with an additional evaluation of whether the cause of death was related to the COVID-19 infection, underlying malignancies, or both. The association of patient outcomes with different demographic variables, disease severity, and treatment strategy (modified or unchanged) was assessed. Cases identified as having benign, non-hematological malignancies were excluded.

The study was approved by the Research Ethics Commission of Hiwa Kurdistan Hospital, and informed consent was obtained from all patients in advance.

RESULTS

A total of 167 patients with different hematological malignancies were enrolled in this study, and their ages ranged from 15–88 years, with a mean of 51.9 ± 18.3 . Most patients were aged 51–65 years (33.5%), and there were slightly more males than females (52.7% vs. 47.3%, respectively). Non-Hodgkin lymphoma ranked as the first malignancy among the studied patients at 19.8%, followed by acute myeloid leukemia (15.6%) and myeloproliferative disorders (15.6%), according to

the distribution of patients by type of malignancy. For disease status, most patients were in complete remission (29.9%), followed by newly diagnosed cases (25.1%), partial remission (21.6%), and on treatment (17.4%). A PCR test was positive in

95.8% of the patients, while a CT scan was positive in 44.9%, and an antibody test in 12.6%. Regarding the severity of COVID-19, 29.9% had mild disease, 35.9% moderate, and 34.1% severe, as shown in Table 1.

Table 1: Clinical characteristics of enrolled patients according to outcome (alive or dead)

Variable	Alive		Dead		Total No. of patients	p value
	No.	(%)	No.	(%)		
Age group (years)						
≤30	21	(77.8)	6	(22.2)	27	.126
31–50	30	(69.8)	13	(30.2)	43	
51–65	49	(87.5)	7	(12.5)	56	
>65	29	(70.7)	12	(29.3)	41	
Sex						
Female	61	(77.2)	18	(22.8)	79	.993
Male	68	(77.3)	20	(22.7)	88	
COVID severity						
Mild	50	(100.0)	0	(0.0)	50	<.001
Moderate	57	(95.0)	3	(5.0)	60	
Severe	22	(38.6)	35	(61.4)	57	
Type of hematological malignancy						
Acute lymphoblast leukemia	14	(63.6)	8	(36.4)	22	.199
Acute myeloblastic leukemia	18	(69.2)	8	(30.8)	26	
Chronic lymphocytic leukemia	17	(81.0)	4	(19.0)	21	
Multiple myeloma	17	(77.3)	5	(22.7)	22	
Myeloproliferative disorder	24	(92.3)	2	(7.7)	26	
Non-Hodgkin lymphoma	27	(81.8)	6	(18.2)	33	
Hodgkin lymphoma	10	(5.9)	0	0	10	
Myelodysplasia	5	(2.9)	0	0	5	
Hairy cell leukemia	2	(1.1)	0	0	2	
Disease status						
Complete remission	39	(78.0)	11	(22.0)	50	.588
Newly diagnosed	31	(73.8)	11	(26.2)	42	
On treatment	23	(79.3)	6	(20.7)	29	
Partial remission	30	(83.3)	6	(16.7)	36	
Relapse	6	(60.0)	4	(40.0)	10	
Treatment strategy						
Unchanged	35	(81.4)	8	(18.6)	43	.451
Modified	94	(75.8)	30	(24.2)	124	

The treatment protocol was modified in 124 patients (74.3%), while 43 patients (25.7%) continued on the same protocol. Regarding

outcomes, 38 patients (22.8%) died. The cause of death was COVID-19 in 30 patients (78.9%), as shown in Table 2.

Table 2: Patient treatment strategy and outcome

Variable	No.	(%)
Treatment strategy		
Modified	124	(74.3)
Unchanged	43	(25.7)
Outcome		
Alive	129	(77.2)
Dead	38	(22.8)
Cause of death (n=39)		
COVID-19	30	(78.9)
Malignancy	2	(5.3)
COVID-19 and malignancy	6	(15.8)

The survival of the COVID-19 patients did not change significantly when treatment was modified in comparison to patients who continued the same treatment protocol. The death rate was significantly ($p < 0.001$) higher among the patients with severe disease (61.4%) compared with mild (0%) or

moderate disease (5.0%). The death rate did not significantly change according to age group, sex, type of disease, and disease status.

Modifying the treatment protocol had no significant effect on the death rate for different demographic and disease variables (Table 3).

Table 3: Effect of treatment strategy on death rate by disease and demographic variable

Variable	Unchanged				Stopped/Modified				p value
	Alive		Dead		Alive		Dead		
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Age group (years)									
≤30	3	(60.0)	2	(40.0)	18	(81.8)	4	(18.2)	.303*
31–50	5	(71.4)	2	(28.6)	25	(69.4)	11	(30.6)	1.000*
51–65	18	(94.7)	1	(5.3)	31	(83.8)	6	(16.2)	.403*
>65	9	(75.0)	3	(25.0)	20	(69.0)	9	(31.0)	1.000*
Sex									
Female	14	(77.8)	4	(22.2)	47	(77.0)	14	(23.0)	1.000*
Male	21	(84.0)	4	(16.0)	47	(74.6)	16	(25.4)	.343
COVID-19 severity									
Mild	16	(100.0)	0	(0.0)	34	(100.0)	0	(0.0)	NA
Moderate	15	(93.8)	1	(6.3)	42	(95.5)	2	(4.5)	1.000*
Severe	4	(36.4)	7	(63.6)	18	(39.1)	28	(60.9)	1.000*
Type of hematological malignancy									
Acute lymphoblast leukemia	1	(100.0)	0	(0.0)	13	(61.9)	8	(38.1)	1.000*
Acute myeloblastic leukemia	1	(50.0)	1	(50.0)	17	(70.8)	7	(29.2)	.529*
Chronic lymphocytic leukemia	9	(81.8)	2	(18.2)	8	(80.0)	2	(20.0)	1.000*
Multiple myeloma	3	(100.0)	0	(0.0)	14	(73.7)	5	(26.3)	1.000*
Myeloproliferative disorder	12	(100.0)	0	(0.0)	12	(85.7)	2	(14.3)	.483*
Non-Hodgkin lymphoma	6	(66.7)	3	(33.3)	21	(87.5)	3	(12.5)	.309*
Disease status									
Complete remission	7	(77.8)	2	(22.2)	32	(78.0)	9	(22.0)	1.000*
Newly diagnosed	5	(100.0)	0	(0.0)	26	(70.3)	11	(29.7)	.303*
On treatment	4	(80.0)	1	(20.0)	19	(79.2)	5	(20.8)	1.000*
Partial remission	19	(82.6)	4	(17.4)	11	(84.6)	2	(15.4)	1.000*
Relapse	0	(0.0)	1	(100.0)	6	(66.7)	3	(33.3)	.400*

* Fisher's exact test

DISCUSSION

Patients with hematological malignancies are presumed to have an increased risk for COVID-19 infection-related fatality or comorbidities due to underlying malignancy and treatment-related immunosuppression. Patients with hematological malignancies, or those receiving chemotherapy or immunotherapy, may be particularly susceptible because of increased immunosuppression and/or immune dysfunction.

The mean age of patients in this study was 51.9 years, with 24.6% being older than 65; however, the fatality rate of patients was not associated with age group, which may be due to the younger age as compared to other studies. Physicians treating elderly patients with hematological malignancies face even more difficulties if these patients are infected with COVID-19 [16]. The effect of age is reflected in the overall case-fatality rate in Italy (7.2%), which is substantially higher than in China (2.3%). When data were stratified by age group, the case-fatality rate in Italy and China appeared very similar for the age group 50–69 years, but rates were higher in Italy among individuals aged 70 years or over, in particular those aged 80 years plus. In Iraq, however, the highest mortality rate was demonstrated among those aged ≥ 50 years who had a severe disease (13.1%) [17, 18].

The current study shows that patients with different hematological malignancies had COVID-19 infection-related fatality (22.8%), similar to early data from China, in which 14–19% of the infected patients developed significant sequelae such as acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure, with approximately 1–4% dying from the disease [19]. Also, case series from China have shown that patients with malignancy are more susceptible to severe infection and mortality from COVID-19. A study by Liang et al. [20] demonstrated that patients with cancer have a higher risk of severe events (a composite endpoint defined as the percentage of patients admitted to the intensive care unit who required invasive ventilation, or died) compared with patients without cancer (39% v. 8% of 1572 patients). Moreover, patients who underwent chemotherapy or surgery in the past month had a numerically higher risk (75% vs. 43%) after adjusting for other risk factors, including age, smoking history, and other comorbidities. This was in addition to the fact that cancer history represented the highest risk for severe events [20].

Another retrospective study from three centers in China showed a mortality rate of 28.6% in patients

with cancer, and patients who received antitumor therapy within 14 days prior to infection had a higher risk of severe infection [21].

Recent analyses from the UK showed that patients with hematological malignancies had a threefold higher risk of hospital mortality due to COVID-19 up to five years from the diagnosis and nearly double the risk thereafter. The higher mortality rate in patients with malignancies was found to be higher for hematological malignancies than for those with solid tumors. There is accumulating evidence that one major mechanism of injury may be a cytokine-release syndrome secondary to severe inflammation, which results in pulmonary damage. Patients with hematologic malignancy may potentially also be more susceptible to cytokine-mediated inflammation due to perturbations in myeloid and lymphocyte cell compartments [22].

This study found that 95.8% of patients were positive via RT-PCR, which is the current gold standard and most widely used assay. The target genes tested include RNA-dependent RNA polymerase (RdRp), open reading frame 1 (ORF1), envelope (E), and nucleocapsid (N) genes of the SARS-CoV-2 genome. Of the studied samples, 3% of the patients with symptoms consistent with a diagnosis of COVID-19 had negative results; these were mostly false-negative due to either improper sampling, degradation of the viral RNA during shipping/storage, low viral loads, incorrect nucleic acid extraction, or the presence of amplification inhibitors and mutation(s) in the RT-PCR target region [23, 24].

Furthermore, the current study confirmed that 44.8% of patients had a chest CT consistent with the imaging characteristics of SARS-CoV-2. Another 10.8% had negative results, in which they had either mild symptoms or the chest CT was performed early in the presentation. The role of chest CT screening is controversial and indeed may play a role in some countries' reporting of a high prevalence of COVID-19 when no PCR was available; routine screening by CT to diagnose COVID-19 may thus not be recommended, and it may be restricted to those who with pulmonary manifestations [25, 26].

There is a plausible concern about treatment modalities for hematological malignancies, as this may expose such patients to a greater risk of SARS-CoV-2 infection. The treatment protocol was modified in 124 patients (74.3%), while 43 patients (25.7%) continued on the same protocol. Deviations from treatment protocols during the COVID-19 pandemic are sometimes unavoidable for logistical reasons, the severity of COVID-19, the duration since

COVID-19 manifestation, and the underlying hematological disease. All these parameters affect the decision to continue the treatment or modify it. However, the treating physicians should remain cautious within the provisions of clinical trial protocols so that the risk benefit balance of the clinical trial remains acceptable; further, the importance of patient monitoring, investigational drug delivery and change of laboratories for diagnostic tests due to access restrictions, as well as the need for social distancing, should not be underestimated [27, 28].

There is tentative evidence that the risk of SARS-CoV-2 infection in cancer patients may be comparable to the general population. This encouraging observation may reflect enhanced precautions, the adoption of protective measures (such as social distancing, hand washing, and masks), and the reconfiguration of cancer care services to maximize patient safety. It is unclear whether there is an increased risk of death associated with specific hematological malignancies or whether there are many predictive risk factors for mortality in cancer patients among all COVID-19 patients. A meta-analysis highlighted the association of chronic diseases including hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and cerebrovascular disease with a risk for developing severe COVID-19 infection among all patients [29].

Overall, current evidence remains insufficient to explain a conclusive association between cancer and COVID-19, as patients with cancer are prone to severe events (admission to the intensive care unit requiring invasive procedures) due to COVID-19. Evidence indicates that overwhelming inflammation and cytokine-associated lung injury could be important triggers of these severe events in patients with COVID-19. There is accumulated evidence that the development of cancer is usually associated with a blunted immune status characterized by overexpressed immunosuppressive cytokines, suppressed induction of proinflammatory danger signals, impaired dendritic cell maturation, and enhanced functional immunosuppressive leukocyte populations, contradictory to the occurrences believed to result in severe events in patients with COVID-19 [30].

In this study, the death rate was significantly ($p < 0.001$) higher among the patients with severe disease (61.4%) compared with mild (0%) or moderate disease (5.0%), and this may be due to the underlying comorbidities not being included, as a proportion of the patients had at least one concurrent risk factor. This is one of the limitations of this study. The survival of patients with COVID-19 was not associated with age group, sex, underlying

hematological disease, or disease status, whether in remission or newly diagnosed. The severity of their infection was the only determinant of mortality, with a case fatality rate of 22.8%, including 78.9% from COVID-19 infection. This may have been due to concomitant immune dysfunction or the effect of COVID-19 and cytokine release syndrome. A study by Mehta et al. showed that 61 (28%) cancer patients died from COVID-19, with a case fatality rate (CFR) of 37% for hematologic malignancies and 25% for solid malignancies. Some 55% of those with lung cancer died from COVID-19, with adjusted CFRs in cancer patients compared to non-cancer patients and other predictors for mortality, which included anemia at the time of infection, elevated LDH, D-dimer, and lactic acid. These correlate with the available data from all COVID-19 patients and may also affect the coagulation system, as shown in both [31] and [32].

Early published case series from China suggested that cancer is comparable to poorly controlled hypertension and diabetes as a risk factor for death from COVID-19. The over-representation of older people with comorbidities and other risk factors in the cancer population is likely to be a confounding factor in this association. Records from the COVID-19 and Cancer Consortium (CCC19) database show that the median age was 66 years, 30% were aged 75 years or older, and 50% were male. Some 39% of patients were on active anticancer treatment, and 43% had active (measurable) cancer. Thirteen percent of patients had died, with race and ethnicity, obesity status, cancer type, type of anticancer therapy, and recent surgery not being associated with mortality [33, 34].

CONCLUSION

The survival of COVID-19 patients with hematological malignancies did not change significantly when the treatment protocol was modified compared with those who continued treatment. Age group, sex, type of hematological malignancy, and disease status did not affect the survival of these patients. The death rate was significantly higher among patients with severe COVID-19 infection in comparison to mild or moderate disease.

CONFLICT OF INTEREST

All authors declare they have had no financial support from any organization that may have an interest in the submitted work, and there is no potential conflict of interest to disclose in relation to this study.

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مرض فيروس كورونا-19 لدى المرضى المصابين بمختلف سرطانات الدم الخبيثة : استراتيجية ونتيجة العلاج: دراسة تجربة عراقية

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الملخص

الخلفية والأهداف: المرضى المصابين بمختلف سرطانات الدم الخبيثة قد يكونون أكثر عرضة للإصابة وبمعدلات أعلى من المراضة والوفيات بسبب فيروس كورونا المتلازمة التنفسية الحادة الوخيمة من هؤلاء في عموم السكان. وهدفت الدراسة لتقييم نتائج فيروس كورونا المتلازمة التنفسية الحادة الوخيمة لدى المرضى المصابين بمختلف سرطانات الدم الخبيثة والذين يخضعون للبروتوكول العلاجي الاصلي أو المعدل. كانت هذه دراسة مرجعية متعددة المراكز أجريت على 167 مريضاً تم تشخيص إصابتهم بمرض فيروس كورونا المتلازمة التنفسية الحادة الوخيمة. المرضى المشمولون بالدراسة هم الذين تم تشخيصهم بمختلف سرطانات الدم الخبيثة وتلقوا العلاج (علاج كيميائي أو مثبث للمناعة). أجريت الدراسة في مراكز مختلفة في جميع أنحاء العراق خلال الفترة من 1 ديسمبر 2020 إلى 1 ديسمبر 2021.

منهجية الدراسة: أجريت هذه الدراسة في 7 مراكز لأمراض الدم في جميع أنحاء العراق من 1 ديسمبر 2020 إلى 1 ديسمبر 2021. منهم 88 من الذكور و 79 من الإناث بمتوسط عمر 51.9 ± 18.3 سنة. كان جميع المرضى مصابين بعدوى مرض فيروس كورونا-19 والتي تم تأكيدها بواسطة فحص جزء خاص من الحمض النووي الريبي عن طريق تفاعل البوليميراز المتسلسل للنسخة العكسية في الوقت الحقيقي (RT-PCR) لعينات مسحة البلعوم الأنفي، والتصوير المقطعي المحوسب للصدر. تم الحصول على البيانات الديموغرافية من ملفات المرضى التي تضمنت نوع سرطان الدم ونوع العلاج (العلاج الكيميائي والعلاج المناعي والداعم) وشدة مرض فيروس كورونا-19 وتعديل العلاج ونتائج المرض بالنسبة للمرضى سواء كانوا أحياء أو أموات تم استبعاد المرضى الذين تم تحديدهم على أنهم مصابون بأورام حميدة أو غير دموية من الدراسة.

النتائج: أظهرت هذه الدراسة أن 88 (52.7%) كانوا من الذكور و 79 (47.3%) من الإناث بمتوسط عمر 51.9 ± 18.3 سنة. تم تعديل البروتوكول العلاجي في 124 مريضاً (74.3%) بينما استمر 43 مريضاً (25.7%) على نفس البروتوكول. فيما يتعلق بنتائج العلاجات، كان 77.2% من المرضى على قيد الحياة في نهاية الدراسة بينما توفي 22.8%. لم يتغير بقاء المرضى المصابين بمرض فيروس كورونا-19 بشكل ملحوظ عندما تم تعديل بروتوكول العلاج مقارنةً بأولئك الذين استمروا في العلاج وفقاً للبروتوكول. كان معدل الوفيات أعلى بشكل ملحوظ بين المرضى الذين يعانون من مرض فيروس كورونا-19 الشديد مقارنة مع المصابين بمرض فيروس كورونا-19 الخفيف والمتوسط (61.4% مقابل 0% و 5.0% على التوالي ($p < 0.001$)).

الاستنتاجات: قد يكون علاج المرضى المصابين بسرطانات الدم الخبيثة أثناء جائحة فيروس كورونا-19 صعبة مع ارتفاع معدل الوفيات في المرضى الذين يعانون من سرطانات الدم الخبيثة والمتزامنة مع جائحة فيروس كورونا-19. لم يتغير بقاء المرضى المصابين بمرض فيروس كورونا-19 بشكل ملحوظ عند تعديل العلاج. لم تؤثر الفئات العمرية والجنس ونوع سرطان الدم والحالة المرضية على بقاء هؤلاء المرضى. كان معدل الوفيات أعلى بشكل ملحوظ بين المرضى المصابين بسرطانات الدم الخبيثة مع فيروس كورونا-19 الشديد بالمقارنة بالمرض الخفيف أو المتوسط. والإيجاز المسبق المنظم باستخدام رسم خرائط المفاهيم يعزز بشكل كبير كفاءة طلاب الطب وتقييمهم الاكلينيكي للمرضى.

الكلمات الدالة: فيروس كورونا-19، سرطانات الدم الخبيثة، النتيجة.