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COVID 19 and febrile neutropenia: Case report and systematic review

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A B S T R A C T

Objectives: In pandemic conditions, patients with febrile neutropenia are also at risk of COVID-19. Aim of this systematic review is to evaluate COVID-19 cases presented with febrile neutropenia and provide information regarding incidence, clinical course and prognosis.
Methods: We systematically searched on COVID-19 and febrile neutropenia cases in PubMed, SCOPUS and Web of Science.
Results: A total of 19 febrile neutropenic patients were analyzed. A male predominance was noted. Eleven cases had hematological malignancies. Fourteen of the cases were previously received chemotherapy. Five patients had severe neutropenia: 3 had hematologic cancer and none died. 17 (89.5%) cases have pulmonary involvement and seven of them had severe disease with acute respiratory distress syndrome (ARDS). Three cases with ARDS were died. 12 of them received G-CSF for treatment. Five cases were developed respiratory failure after G-CSF use. Overall mortality was 15.8%, while death was not observed in patients without malignancy and solid organ tumors, the mortality rate was 27% in cases with hematological malignancies.
Conclusion: In ongoing pandemic, febrile neutropenic patients should be precisely evaluated for COVID-19 disease. It should be remembered that there may not be typical signs and symptoms and laboratory findings of COVID-19 disease because of the immunosuppression.

1. Introduction

The COVID-19 epidemic, which started in Wuhan, China [1], quickly turned into a pandemic that affected all countries [2]. The virus is highly transmissible and spreads person to person during close contact via respiratory droplets. The disease, which progresses in a clinical picture ranging from mild to death, causes severe disease especially in patients with diabetes mellitus, chronic lung disease, hypertension, chronic heart disease, transplant patients and cancer [3]. Although patients with a mild disease generally recover within 2 weeks, the disease could be complicated with acute respiratory distress syndrome and cytokine storm that can lead to multiple organ failure and death [4]. Cancer patients infected with SARS-CoV-2 have a higher risk of admission to intensive care unit, requiring invasive ventilation and death compare with patients without cancer [5,6]. Cancer patients have immunosuppression both from the malignancy itself and also from the effects of treatment, especially the patients on active cancer treatment within the 30-day period before the COVID-19 infection. Patients with cancer have higher likelihood of increased age and co-morbidities. Cancer is associated with a higher risk of mortality and admission to intensive care unit (ICU) [5]. Chemotherapy that suppresses the immune system also increases the risk of those complications in COVID-19 [7]. Chemotherapy-induced febrile neutropenia is life-treating condition. In pandemic conditions, patients with febrile neutropenia are also at risk of COVID-19.

The information about the incidence and management of COVID-19 in febrile neutropenic patients is limited. To our knowledge, no previously published systematic reviews have reported the association between COVID-19 and febrile neutropenia and prognosis. We have present two patients and reviewed the current literature to evaluate COVID-19 cases presented with febrile neutropenia and provide information regarding incidence, clinical course and prognosis.

2. Methods

The protocol for this review was published in PROSPERO (International Prospective Register of Systematic Reviews) under registration CRD42021269070.

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2.1. Search strategy

Literature were reviewed by using a protocol the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [8]. Published studies index in multiple electronic databases (PubMed, SCPOUS and Web of Science (WoS)) were searched by two authors (TK and AD) independently using the key terms "COVID-19" and "febrile neutropenia" from December 1, 2019 until October 3, 2021. No restriction on publication language and country of origin was applied.

2.2. Eligibility criteria

Studies or case reports or case series included in the systematic review fulfilled the following criteria: (1) Confirmed of probable COVID-19 cases, (adult cases ≥18 years old), (3) suspected febrile neutropenia, (3) Inpatient cases. Pediatric cases and cases had neutropenia without fever were not included. Conference abstracts, reviews and editorials were excluded from this review.

2.3. Case definition

Target population was confirmed and COVID-19 cases with febrile neutropenia. WHO case definition was used for diagnosis of COVID-19 [9]. According to EORTC; febrile neutropenia was defined as chemotherapy-induced neutropenia (absolute neutrophil count (ANC) < 1000 cells/μL) and fever (single oral temperature ≥38.3 °C or ≥38 °C sustained over 1 h). Also severe neutropenia as ANC <500/μL, and profound neutropenia as < 100/μL were accepted. Fever in neutropenic patients is defined as a single oral temperature of ≥38.3 °C (101 °F) or a temperature of ≥38.0 °C (100.4 °F) sustained over 1 h [10]. If the number of neutrophils was not specified in the publication and the authors wrote the cases had neutropenia, then the cases were accepted as neutropenic.

2.4. Screening process

All searched articles were selected if the titles and/or abstracts were related to study goal. Two independent authors (T.K. and A.D.) reviewed the full text of the articles. The reference lists of all included reports were also screened for eligibility. Reports without clinical and laboratory features of individual cases were not included. Discrepancies were resolved through discussion with third author (H.L.) and consensus (Fig. 1).

2.5. Quality assessment

Thirteen-item CARE Guidelines used to assess the quality of the included each case reports [11].

2.6. Data extraction and statistics

A standardized data extraction form was used. Following items (1) first author's name, (2) country of origin, (3) study size (number of cases), (3) gender, (4) type of malignancy, (5) co-morbidities (6) clinical presentation, (7) associated infections, (8) pulmonary involvement, (9) neutropenia status, (10) microbiological isolates, (11) treatment and (12) outcome were extracted by two authors (TK and AD). Then discrepancies were resolved by discussion between all the authors. Descriptive statistics are limited to mean (±SD) and percentages performed with SPSS software, version 20.0 (IBM Corp, Armonk, NY).

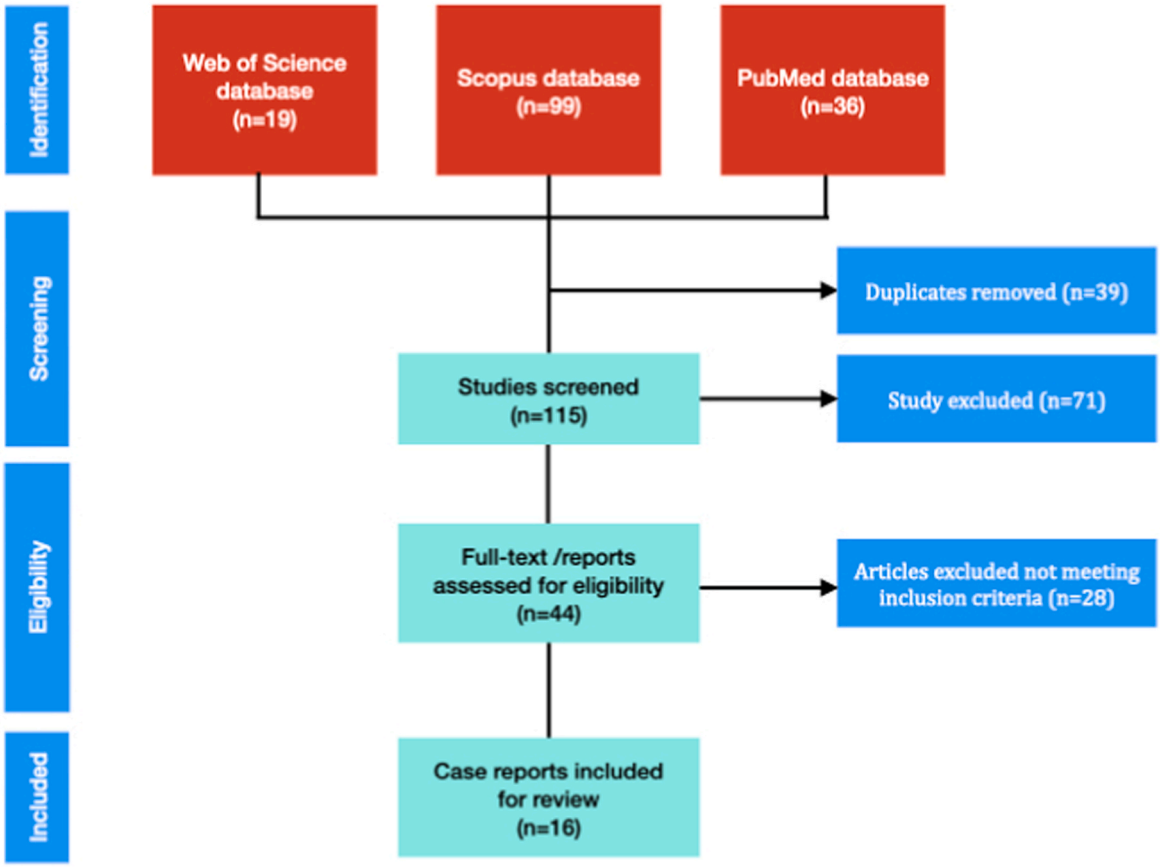
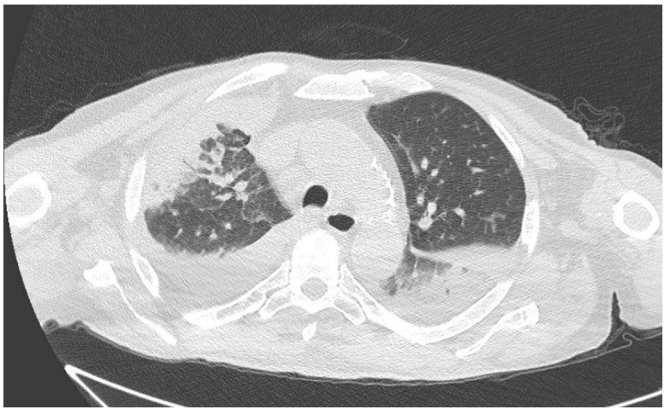


Fig. 1. Study selection and characteristics, based on the PRISMA 2020 Standard for Systematic Reviews.

3. Results

3.1. Case 1

A 78-year-old male diagnosed with polycythemia vera transformed into acute myeloid leukemia was admitted with fever and cough emerged after chemotherapy. Body temperature was 39C. Leukocyte count was 320/mm^3 (neutrophils 140/mm^3 and lymphocytes 160/mm^3). Galactomannan antigens in the blood and acid-fast bacilli in the pulmonary samples (repeated three times) were negative. COVID-PCR study was positive. In thoracic CT, bilateral pulmonary infiltrations and pleural effusions were noted (Fig. 2a). Additionally, right lung revealed a pulmonary abscess. A surgical intervention could not be performed due to the poor performance score of the patient. He has initiated meropenem treatment empirically. Sputum culture yielded *Pseudomonas aeruginosa* with intermediate sensitivity to meropenem and full sensitivity to piperacillin/tazobactam. The treatment was switched to piperacillin/tazobactam. He was also given granulocyte-colony stimulating factor (G-CSF) (for his neutropenia), methylprednisolone 160 mg/day, furosemide, enoxaparin, and favipiravir (for the COVID-19 disease). Despite nasal oxygen support, he developed respiratory distress and was transferred to ICU. An atelectasis was observed on the right lung (Fig. 2b). He required intubation and invasive mechanical ventilation. He, then died of hypotension and multiple organ failure.



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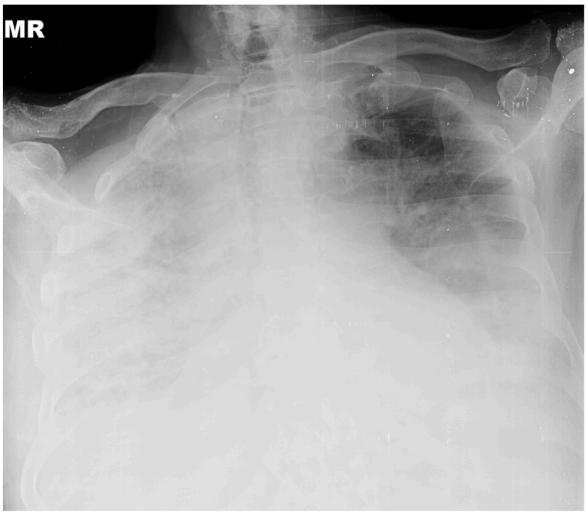

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Fig. 2. a. Lung CT showing bilateral pleural effusion and right-sided peripheral pulmonary infiltration.
Fig. 2b. Plain X-ray showing the atelectasis on the right lung.
Fig. 3a. Pulmonary infiltration on chest CT.

3.2. Case 2

A 50-year-old female with diffuse large B cell lymphoma and type 2 diabetes was admitted with fever and shortness of breath. She was applied bone marrow transplantation three months ago. A COVID-PCR study was obtained and resulted positive. Favipiravir and methylprednisolone (250 mg/day) were initiated. Pulmonary infiltrations increased (Fig. 3a) and she was transferred to ICU with respiratory distress. Complete blood count yielded pancytopenia with a leukocyte count of 1200/mm^3 (neutrophils 770/mm^3). She was applied continuous positive airway pressure. G-CSF was given. She was also given piperacillin/tazobactam and clarithromycin after obtaining blood cultures.

Blood cultures yielded coagulase-negative staphylococci and vancomycin was added. Nasal secretion cultured *Candida kruseii*. She developed ptosis on the right eye and periorbital edema and necrosis. (Fig. 3b). A diffusion MRI of the right eye showed diffusion restrictions of the optic nerve, right ocular proptosis, diffuse edema in intracoronal, extracoronal fatty plains of the right eye. Right maxillary sinus, bilateral ethmoid sinuses and frontal sinus showed air-fluid levels and mucosal thickenings. Right orbital medical wall was intact (Fig. 3c). An orbital angiographic CT showed complete obstruction of right ophthalmic artery (Fig. 3d). Considering invasive fungal infection probability, she was given caspofungin. The respiratory distress increased, and she required intubation with mechanical ventilation. She died of respiratory failure.

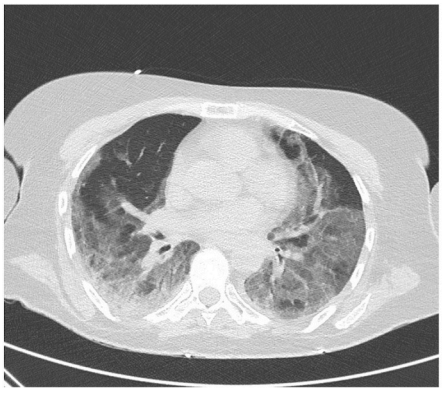
3.3. Review of published cases of COVID-19 with febrile neutropenia

Fig. 1 illustrates the flow diagram of publication selection. A total of 115 titles and abstracts were reviewed, and 44 full articles were retrieved. 16 case reports were eligible for review (Table 1). 19 cases were reported [12–27]. 12 countries represented (USA (n = 3); India, and UK (n = 2); Argentina, Belgium, China, Italy, Japan, Pakistan, Qatar, Spain and Ukraine (n = 1).

A total of 19 febrile neutropenic patients with COVID PCR positive were analyzed. A male predominance noted with male to female ratio is 15/4. Age was 47 ± 19.6 (23–76). 11 of the cases had hematological malignancies (leukemia n = 9, lymphoma n = 2), 6 of them had solid organ tumors, one had a history of kidney transplantation, and one was immunocompetent. Fourteen of the cases were previously received chemotherapy. Five patients had severe neutropenia: 3 had hematologic cancer and none died.

17 (89.5%) cases have pulmonary involvement and seven of them had severe disease with acute respiratory distress syndrome (ARDS). Three cases with ARDS were died. Seven of the cases received steroids and 12 of them received G-CSF for treatment. Five cases were developed respiratory failure after G-CSF use and the failure was suggested to associate with neutrophil to lymphocyte ratio (NLR) [19,22,24]. In their case series, Nawal et al. reported respiratory decline in all three patients with NLR of >5 at 72 after administration of GCSF. Jain et al. [19] reported a possible G–CSF–induced ARDS on the same day of G-CSF administration, with a sudden increase in neutrophils (10-fold) and also in NLR (5-fold). In the report of Mertens et al. [22] an association between increase in neutrophil count following G-CSF administration and concurrent worsening of respiratory failure/pulmonary infiltrates was described.

Overall mortality was 15.8%, while death was not observed in patients without malignancy and solid organ tumors, the mortality rate was 27% (3/11) in cases with hematological malignancies. Only one of the three deaths was given antifungal therapy. Four of the cases (all with hematologic malignancy) were intubated and three of them were died.



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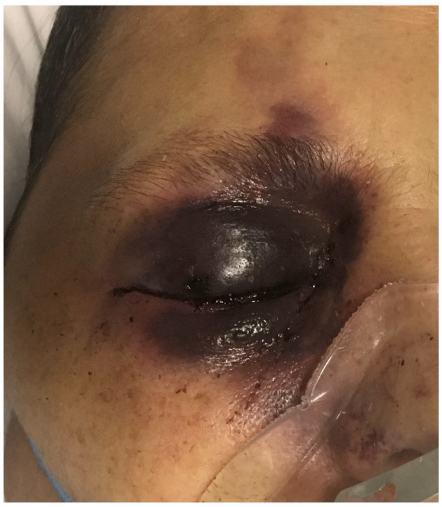

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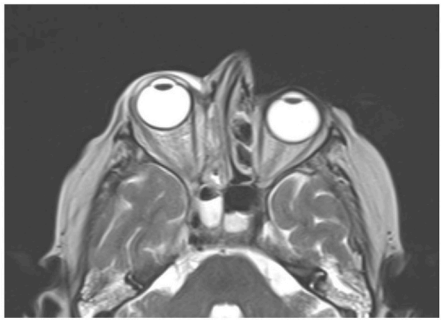

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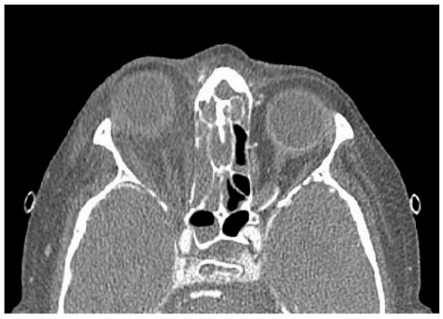

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Fig. 3. b. Right periorbital edema and necrosis.
Fig. 3c. A diffusion MRI of the right eye showing diffusion restrictions of the optic nerve, right ocular proptosis, diffuse edema in intracoronal, extracoronal fatty plains of the right eye.
Fig. 3d. An orbital angiographic CT showing complete obstruction of right ophthalmic artery.

4. Discussion

To our knowledge, current study represents the first systematic review of COVID-19 infections in adult febrile neutropenic patients. The study revealed that the rate of adult respiratory distress syndrome (ARDS) is high, the course of disease is severe; and fatality rate is high among febrile neutropenic patients with hematological cancer.

Febrile neutropenia results as a complication of cancer chemotherapy. Bacterial and fungal infections are a cause of significant morbidity and mortality in neutropenic patients. The information about COVID-19 disease in patients with neutropenia due to chemotherapy is limited. Yarza R et al. [28] reported bilateral pulmonary involvement, ARDS, and severe neutropenia as independent risk factors of mortality among cancer patients. However, fever was not considered among neutropenic patients in the study. Our review revealed survival of 5 patients. COVID-19 disease follows a wide spectrum of severity ranging from mild upper respiratory tract infection to severe respiratory disease needing respiratory support with mechanical ventilation in ICU. In our analysis, most of the patients needed nasal oxygen support while 4 developed ARDS, 3 required intubation with mechanical ventilation while 1 needed non-invasive mechanical ventilation. Our findings also support that development of ARDS is a main risk factor for the mortality.

During the course of COVID-19, in addition to the development of ARDS, other potentially fatal complications of atelectasis [29] and pneumothorax [30] can be seen. Both complications cause further worsening of the clinical situation by decreasing the pulmonary capacity. Our first patient recorded sudden decrease of oxygen saturation with development of atelectasis and required intubation with mechanical ventilation and then followed by death. A sudden decrease in respiratory functions and development of respiratory failure need a search for pulmonary complications by radiology. Although computed tomogram gives more detailed information, transfer of the patient to radiology unit may not be possible. At least, a bedside plain chest X-ray may be informative.

COVID-19 disease emerges as another risk factor of mortality for cancer patients in addition to the immunosuppression due to the disease itself and also to chemotherapy. The mortality of COVID-19 is higher among cancer patients. Our study confirmed this higher rate. Catherine Garnett et al. [31] reported 56% of mortality in their series of 32 patients with hematologic cancer. This rate was reported as 37% in the series of Mehta V et al. [32] In the systematic review and meta-analysis of Vijenthira A et al. [33] in-hospital mortality was 34% among 3377 patients with hematologic cancer patients $\geq$60 year-old had a higher mortality (RR, 1.82; 95% CI, 1.45–2.27; N = 1169). In our analysis, three patients have died, and we did not observe an accumulation in certain age groups.

The risk of fungal infections is associated with the duration of neutropenia in febrile neutropenic patients and the risk increases after 14 days [34]. Underlying disorders including diabetes and cancer and steroid use increase the risk of fungal infection in COVID-19 disease [35–37]. In our second case, we considered fungal infection with clinical findings and added caspofungin to the treatment. Nasal secretion cultured *C. kruseii*. *C. kuresii* infections are rarely reported among neutropenic patients and its prognosis is usually poor [38]. It has not been reported among patients with COVID-19, while it has been described in a patient with MERS-CoV causing a fatal pneumonia [39]. Orbital edema

Table 1
Clinical and laboratory characteristics, treatment, and outcomes in febrile neutropenic patients with COVID-19.

Author(s)	Country	Age (years)	Gender	Underlying disease	Systemic diseases	Pulmonary Involvement of COVID-19	Ventilation status	Leukocyte count	Neutrophil count	Lymphocyte count	Ferritin	d-dimer	Crp	Chemotherapy	Steroid Use	Complication	G-CSF use	Worsening after G-CSF	Antibiotic use	GM	Antiviral and antifungal use	Tocilizumab use	Outcome
Abdalhadi AM, et al. [12]	Qatar	65	M	Chronic Myeloid Leukemia	No	Bilateral consolidation and pleural effusion, ARDS	NIMV	3800/μL	900/μL	2800/μL	1199		74.6 mg/L	Yes	Yes	No	Yes		Piperacillin/tazobactam	NA	Hq 400 mg, oseltamivir, then lopinavir/ritonavir	Yes	Alive
Al-Makki A, et al. [13]	USA	33	F	Kidney transplant	Renal transplant, HT, Asthma, Obesity	Bilateral patchy peripheral interstitial and airspace opacities with air bronchograms	Nasal	4000/μL	800/μL					No	Yes	No	No		Cefepim, azitro	NA	Hq	No	Alive
Benedetti MF, et al. [14]	Argentina	23	M	B cell Acute lymphoblastic leukemia	No	multiple bilateral GGO, CPP, PNC with an air-bronchogram at the level of the right posterior basal segment of the lung	Intubated		NA					Yes	No	No	No NA		Meropenem, colistin, amikasin, vancomycin	Serum. 0.9 TA. 4.2	Voriconazole	No	Death
Butt A, et al. [15]	Pakistan	24	M	T-cell acute lymphocytic leukemia	No	Severe ARDS	Nasal	<500/μL	<500/μL		22 ng/mL			Yes	No	2 months later cerebral vein thrombosis	Yes		NA	8.07(cutoff>0.7)	Voriconazole	No	Alive
De Giorgi U, et al. [16]	Italy	33	M	Metastatic testicular germ cell cancer	No	No	Nasal		<1000/μL				191 mg/dL	Yes	No	No	No		Levofloxacin, piperacillin/tazobactam	NA	Ritonavir, darunavir, Hq	No	Alive
Devi YM, et al. [17]	İndia	76	M	No	HT, DM	X-ray: bilateral fluffy opacities in all the zones, more in the periphery	Nasal		390/μL					No	Yes	No	Yes		Azitromycin, amoxicilin, piperacillin/tazobactam	NA	Remdesivir	No	Alive
Figuero-Perez L, et al. [18]	Spain	76	M	Metastatic lung adenocarcinoma	COPD	X-ray. Diffuse infiltrates	Nasal		430/μL				24.4 mg/dL	Yes	No	No	No		Piperacillin-tazobactam		No	No	Alive
Jain A, et	India	30	M	Chronic myelomonocyti	No	Yes ARDS	Intubated	451,000/	0	10,000/μL		Elevated		Yes	Yes	No	Yes	Yes	Azithromycin	Negative	Hq	No	Death

al. [19]				c leukemia				µL															
Kulinich HV, et al. [20]	Ukraine	72	F	Endometrial Leiomyosarcoma	HT	Polysegmental pneumonia involving less than 25 % of the lungs	Nasal		509/µL	380 / µL				Yes	Yes	No	Yes		Fluoroquinolones, macrolides	NA	No	No	Alive
Li Q, et al. [21]	China	26	M	Primary mediastinal Large B-Cell Lymphoma	No	Bilateral opacities and pleural effusion	Nasal		890/µL	680 / µL				Yes	NA	No	Yes		Meropenem, linezolid, azithromycin		Ganciclovir, oseltamivir, posaconazole. arbidol hydrochloride and LHQW capsule		Alive
Mertens J, et al. [22]	Belgium	54	M	Nasopharyngeal carcinoma	Type 2 DM, HT, and rheumatoid arthritis	Mild opacities, ARDS	NIMV		510/µL		5452	3700	138	Yes	Yes	Paradoxical IRIS	Yes	Yes	Piperacillin / tazobactam	NA	Hq		Alive
Nagai K, et al. [23]	Japan	67	M	Pancreatic cancer	Ground-glass opacity in the peripheral lesions of both lungs	Yes	Nasal		560/µL				36.2	Yes	NA		Yes		Piperacillin / tazobactam	NA	Favipiravir, lopinavir/ ritonavir		Alive
Nawar T, et al. [24]	USA	65	M	Acute myeloid leukemia	HT, DM (type 2), hepatitis C	ARDS	Intubated		300/µL		2790	120	60.9	No	NA	Received G-CSF and developed severe disease from COVID-19 within 72 hours of administration	Yes	Yes	Aztreonam, vancomycin	NA	Hq		Death
		35	F	Mediastinal diffuse large B-cell lymphoma	None	Bilateral opacities	Nasal		600/µL		5	30	4.9	No	NA		Yes	Yes	Piperacillin-tazobactam	NA	Hq		Alive
		58	F	Invasive ductal carcinoma of the breast	Obesity	ARDS	Intubated		600/µL		2056	400	154.5	No	NA		Yes	Yes	Cefepime	NA	Hq		Alive
O'Nions J, et al. [25]	UK	24	M	Acute myeloid leukemia	None	Multiple consolidations	Nasal							Yes	No							No	Alive
		54	M	T-cell lymphoblastic leukemia	None	No	Nasal							Yes	No							No	Alive
Spencer HC, et al. [26]	USA	51	M	NK-cell large granular lymphocytic leukemia	No	Bilateral interstitial infiltrates	Nasal		550/µL					Yes	No		yes		Cefepime, Azithromycin	NA			Alive
Wilson AC, et al.[27]	UK	27	M	Acute myeloid leukemia	No	ARDS	Intubated		<0.5/µL					Yes	Yes								Alive

Current case reports	Turkey	78	M	Acute myeloid leukemia	No	bilateral pulmonary infiltrations and pleural effusions	Intubated	320	140	160				Yes	Yes	Pulmonary abscess	Yes	Yes	Piperacillin-tazobactam			No	Death
		50	F	diffuse large B cell lymphoma	DM	bilateral pulmonary infiltrations	Intubated	1200	770	430				Yes	Yes	Orbital fungal infection	Yes	No	Piperacillin-tazobactam, clarithromycin		Caspofungin , favipiravir	No	Death

GM: galactomannan, M: male, F: female, ARDS. Acute respiratory distress syndrome, NIMV: non-invasive mechanical ventilation, Hq: hydroxychloroquine, DM: diabetes, mellitus, HT: hypertension, IRIS: immune reconstitution inflammatory syndrome, LHWQ: Lian Hua Qing Wen, USA: United States of America, UK: United Kingdom, COPD: chronic obstructive pulmonary disease, G-CSF: granulocyte-colony stimulating factor, NK: natural killer, GGO: ground glass opacities; CPP: crazy paving pattern; PNC: peripheral nodular consolidations, TA: tracheal aspirate.

GM: galactomannan, M: male, F: female, ARDS. Acute respiratory distress syndrome, NIMV: non-invasive mechanical ventilation, Hq: hydroxychloroquine, DM: diabetes, mellitus, HT: hypertension, IRIS: immune reconstitution inflammatory syndrome, LHWQ: Lian Hua Qing Wen, USA: United States of America, UK: United Kingdom, COPD: chronic obstructive pulmonary disease, G-CSF: granulocyte-colony stimulating factor, NK: natural killer, GGO: ground glass opacities; CPP: crazy paving pattern; PNC: peripheral nodular consolidations, TA: tracheal aspirate.

developing during the course of COVID-19 infection necessitates the use of culture and orbital MRI to rule out the invasive fungal infections.

In this systematic review, we noted that respiratory distress developing after G-CSF use was described in five patients [19,22,24]. Another patient with renal transplant and COVID-19 disease associated with neutropenia without fever has been reported to experience deterioration after G-CSF use [40]. COVID-19 patients with pulmonary involvement may experience acute respiratory failure and increase in pulmonary infiltration upon leukocyte recovery [41]. In pathogenesis of pulmonary damage in COVID-19, neutrophil infiltration in pulmonary capillaries, acute capillaritis with fibrin deposition, and extravasation of neutrophils into the alveolar space were shown in autopsy samples [42]. he neutrophil to lymphocyte ratio (NLR) on the other hand, has been reported as a significant predictor of in-hospital mortality of COVID-19 patients [43]. It is not clear whether the absolute increase of neutrophils or that of NLR in patients with worsening pulmonary functions after G-CSF administration. Despite this risk of G-CSF use, since the benefits outweigh the harms, ESMO guideline recommends its use [44]. In COVID-19 patients with febrile neutropenia, G-CSF can be used carefully and the patients should be assessed individually [45,46].

A specific antiviral effective against COVID-19 disease is lacking. Current treatment options include steroid use and oxygen support. All patients in this series were given steroids and oxygen support. In severe patients, non-invasive and invasive supports were also used. Since the case reports include a 2-year period of pandemic, therapeutic options thereafter shown to be ineffective including hydroxychloroquine, oseltamivir, gancyclovir, and lopinavir/ritonavir were also used. Polypharmacy is an ongoing challenge in COVID-19 disease and febrile neutropenia further increases this challenge.

This review showed that the reports of COVID-19 infection in febrile neutropenic patients are limited. A clinical study describing and reporting COVID-19 infection in febrile neutropenic patients is lacking. COVID-19 pandemic affected health care adversely in every country. Jazieh AR et al. [47] showed in their cross-sectional study including 356 centers from 54 countries that 55.3% of the centers decreased their health care services, and in 46.3% of the centers, more than 10% of the patients could not receive at least one cycle of chemotherapy. Riera et al. [48] in their systematic review of 62 studies, noted 38 different categories of delays and disruptions with impact on treatment, diagnosis, or general health services of cancer patients during COVID-19 pandemic. A surveillance study showed that 66% of cancer patients had a high level of fear from COVID-19 [49]. Therefore, for the continuum of cancer management during COVID-19 pandemic, certain number of beds should be reserved for cancer patients. The thread and fear of COVID-19 infection may have caused delays and disruptions of hospital admission among cancer patients and interrupted the treatment.

The main shortage of the study is including few numbers of patients. Secondly, there is no study comparing febrile neutropenic patients with or without COVID-19 disease. Therefore, comparative prospective studies are needed to describe the factors determining mortality.

In conclusion; pulmonary complications determine mortality in both febrile neutropenia and in COVID-19 disease. In ongoing pandemic, febrile neutropenic patients should be precisely evaluated for COVID-19 disease. It should be remembered that there may not be typical signs and symptoms and laboratory findings of COVID-19 disease because of the immunosuppression. COVID-19 PCR study and chest imaging studies are contributory and can provide timely diagnosis and treatment.

Contribution

All authors designed the research, contributed to data collection analyzed the data and wrote the manuscript.

Declaration of competing interest

All authors declare no competing financial interests.

Appendix A. Supplementary data

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