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HEMATOLOGICAL DISEASES AND COVID-19

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Abstract: Hematologic neoplasms are a heterogeneous group of cancers comprising several subgroups of neoplasms. So far, despite major epidemiological concerns about quality of care, limited data are available for patients with hematologic malignancies. To retrospectively analyze the epidemiological, clinical and hematological characteristics of patients at the Hospital Universitário de Vassouras, Rio de Janeiro, Brazil during the COVID-19 pandemic. In addition, it aims to report the most prevalent hematological diseases in the municipality. In addition, it is important to consider that patients with hematological malignancy are immunocompromised. It is expected that the present study will reveal that there is an increased risk of serious events related to COVID-19 (ICU admission, need for MV or death) in patients with hematologic malignancy compared to patients infected with COVID-19 without cancer. due to the high vulnerability of patients with hematological malignancies in the current pandemic. It was observed that there is an increased risk of serious events related to COVID-19 (ICU admission, need for MV or death) in patients with hematologic malignancy compared to patients infected with COVID-19 without cancer due to the high vulnerability of the patients. patients with hematologic malignancies in the current pandemic. It was therefore noted that clinicians must pay close attention to treating COVID-19 patients with hematologic malignancy. Telephone screening or other online technologies must be used to verify the need for treatment or follow-up at inpatient or outpatient clinics. In non-life-threatening patients, hospitalization must be postponed. Patients with fever or other symptoms that may be related to COVID-19 must be tested for SARS-CoV-2 RNA and they must not be accepted into the hematology ward before the possibility of COVID-19 has

been ruled out.

Keywords: Hematologic malignancies, Hodgkin's lymphoma, Leukemia, Multiple myeloma, Non-Hodgkin's lymphoma, COVID-19.

INTRODUCTION

In late December 2019, in the city of Wuhan, People's Republic of China, pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was described for the first time (WHO, 2020). As the situation rapidly evolved, the coronavirus disease 2019 (COVID-19) pandemic began (CATTANEO et al. 2020). One year after the first case, in April 2021, >130 million cases of COVID-19 were reported, of which 2.8 million died. Hematologic malignancies (HMs) were found to be prevalent in 2% of COVID-19 patients overall (DESAI et al. 2020). It is estimated that there were over 250 million confirmed cases of COVID-19 and over 5 million deaths as of November 20, 2021 (JOHNS HOPKINS, 2021).

MHs are a heterogeneous group of malignancies that are essential contributors to the global burden of cancer (GBD et al. 2020). They are commonly classified by their four common subtypes: leukemia, Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) (WHO, 2020; HEMMINKI et al. 2020). The diversity of mortality, incidence, origin and pathogenesis of leukemia depends on its subtype, which is generally classified as lymphoid and myeloid according to the World Health Organization (WHO) classification for hematopoietic and lymphoid tissue tumors (WHO, 2020; ABREU et al. 2007). In 2018, there were 407,000 incident cases of leukemia and 309,000 deaths (KEYKHAEI et al. 2020; BRAY et al. 2018). Furthermore, in 2017, Hodgkin lymphoma, NHL, and MM accounted for 1.4, 7.0, and 2.3 million disability-adjusted life years, respectively (GBD et al. 2020). Therefore, given the increasing trend, more intense attention must be given to these patients.

The incidence of hematologic malignancies varies based on subtypes, age, sex, and socioeconomic status. For example, between 1990 and 2017, a remarkable decrease in the incidence of acute lymphocytic leukemia (ALL) and chronic myeloid leukemia (CML) was discovered; however, the incidence rate of chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) has increased considerably in most countries (DONG et al. 2017). The incidence of HL cases increased by 38.6% from 1990 to 2017 (ZHOU et al. 2019). The age-standardized incidence rate (ASIR) of leukemia was higher in men than in women (DONG et al. 2017). Furthermore, it was revealed that the incidence of leukemia has only increased in people aged ≥ 70 years (DONG et al. 2017). In terms of socioeconomic status, the highest incidence of leukemia occurred in the medium-high Sociodemographic Index (SDI) region (DONG et al. 2017). As a result, proper prioritization of resources is crucial to reduce the undesirable effects of the increased incidence of HMs.

Overall, in western countries, the overall incidence of hematologic malignancies appears to be increasing, but it is very difficult to consistently and uniformly describe epidemiological behavior, especially during the COVID-19 pandemic (ZHANG et al. 2020; YANG et al, 2020; MARTÍN-MORO et al. 2020). In Brazil, there is a diversity of peoples with a much greater degree of heterogeneity in lifestyle habits and disease risk, as well as in cancer incidence and mortality (general or site-specific) (HE et al. 2020). In addition, there is no single Brazilian reporting system or registry for hematological cancers, so estimating the exact number of patients is difficult. Furthermore, the comparison of reported incidences by various Brazilian

registries may be insufficient because the population may be predominantly urban or rural, or because there are differences in the methodology and accuracy of the registry.

JUSTIFICATION

The control and prevention of hematologic malignancies will require a better understanding of the origins of the diseases. Avoiding exposure to risk determinants would result in a reduction in cancer risk. What little we know about risk factors has not yet been translated into consistent attempts to prevent hematologic disease. Some general consideration, however, can be made. Local prevention strategies become more effective; since we already know that avoiding exposure to radiation and benzene will reduce the risk of leukemias. Eradicating or restricting the use of organochlorines may in the long term result in a reduction in the incidence of NHL. About 20% of adult cases of acute myeloid leukemia are linked to smoking and prevention is therefore possible here. HIV infection is clearly preventable and other infectious agents associated with NHL can also be the target of preventive measures and this way, the best prevention and control strategies can be designed.

MATERIAL AND METHODS

A non-systematic literature review was carried out until November 1, 2022. Based on the terms: "hematology" AND "epidemiology" in the following databases: PubMed, Scielo, LILACS. Articles originally published in English were considered eligible. Articles published in the year 2020 to 2021 were included, focusing on analyzing the clinic of COVID-19 in hematology with data from the current scientific literature. Alternatively, other studies selected jointly by the authors were included to reference complementary data from the review. These studies, in turn, were not necessarily listed in previously consulted databases and publication dates prior to 2019 were considered suitable.

RESULTS

The study performed by Yigenoglu et al. in Turkey used data from 188,897 laboratory-confirmed COVID-19 patients diagnosed between March 11, 2020 and June 22, 2020. All COVID-19 patients with hematologic malignancy (n=740) were included in the study and an age, sex, and comorbidity-matched cohort of COVID-19 patients without cancer (n=740) in a 1:1 ratio was used for comparison. Non-Hodgkin's lymphoma (30.1%), myelodysplastic syndrome (19.7%), myeloproliferative neoplasm (15.7%) were the most common hematologic neoplasms. Severe and critical illness rates were significantly higher in patients with hematologic malignancy compared with patients without cancer=0.001). Hospital and intensive care unit (ICU) admission rates were higher in patients with hematologic malignancy compared with patients without cancer (P = 0.023, P = 0.001, respectively). Hospital and ICU length of stay was similar between groups (P = 0.7, P = 0.3, retrospectively). The rate of mechanical ventilation (MV) support was higher in patients with hematologic malignancy compared with the control group (P = 0.001). The case fatality rate was 13.8% in patients with hematologic malignancy, and was 6.8% in the control group (P = 0.001). This study reveals that there is an increased risk of serious COVID-19-related events (ICU admission, MV support, or death) in patients with hematologic malignancy compared to COVID-19 patients without cancer and confirms the high vulnerability of patients with malignancy. hematology in the current pandemic (YIGENOGLU et al. 2021).

The prevalence of cancer in patients with COVID-19 is uncertain. Previous studies from China reported that 1% to 2% of patients with COVID-19 had cancer, and a study from the

United States reported that 6% of hospitalized patients with COVID-19 had cancer. In Lombardy, Italy, they observed that 8% of patients admitted to the ICU for COVID-19 had cancer. In a meta-analysis, the prevalence of cancer was 2% among patients with COVID-19 (DESAI et al. 2020; GRASSELLI et al. 2020). Although there are reports on the prevalence of cancer among patients with COVID-19, data on the prevalence of hematologic malignancies among patients with COVID-19 are very limited. In our study, we found that 0.39% of laboratory-confirmed COVID-19 patients had hematologic malignancy. The most common hematologic malignancies in patients with COVID-19 were NHL (30.1%), followed by MDS (19.7%).

There is also less existing knowledge in the literature about the disease course in COVID-19 patients with hematologic malignancies. In a previous study, researchers analyzed data from 105 cancer patients hospitalized for COVID-19 and compared their results with patients without cancer. Among 105 COVID-19 patients with cancer, nine had hematologic malignancy. When compared with non-cancer patients, they found that cancer patients had higher mortality rates, higher ICU admission rates and a more severe course of COVID-19 and had a higher rate of MV support. In addition, they observed that patients with hematologic malignancies, lung cancer, and metastatic cancer had the highest frequency of serious events (DAI et al. 2020). In a study carried out by Mehta et al. ICU admission rate and MV support rate were higher in patients with hematologic malignancy (26%) compared with patients with solid tumors (19%); however, this did not reach statistical significance (MEHTA et al. 2020). In our study, a severe course of COVID-19 was observed in 15.5% of patients with hematologic malignancy, while it was observed in 13% of patients without cancer. Furthermore, the rate of critically ill COVID-19 patients was 13.2% among patients with hematologic malignancy, while it was 6.6% among patients without cancer. We found that rates of serious and critical illness were significantly higher in patients with hematologic malignancy compared with patients without cancer. Rates of ICU and hospital admission and MV support were higher in COVID-19 patients with hematologic malignancy compared with the control group (SICA et al. 2021).

In a previous study, the mortality rate in myeloid neoplasms (MDS/AML/MPN) was higher than in lymphoid neoplasms (NHL/LLC/LLA/MM/HL) (43% vs 35%), (MEHTA et al. 2020). In contrast to their results, we found no significant difference between lymphoid neoplasms (NHL, HL, ALL, CLL, HCL, MM) and myeloid neoplasms (AML, MDS, MPN, CML) in relation to CFRs. In their study, there were 14 patients with myeloid neoplasms and 40 patients with lymphoid neoplasms; however, in our study, there were 332 patients with myeloid neoplasms and 408 patients with lymphoid neoplasms, so this contrast between the two studies can be attributed to the different sizes of the studies.

CFR in COVID-19 patients with hematologic malignancy also differs in limited published studies. In a study by Mehta et al, CFR in COVID-19 patients with hematologic malignancy was 37%. Also in their study, they compared the outcome of hospitalized patients with COVID-19 with hematological malignancy to health professionals with COVID-19 (MEHTA et al. 2020). They found that hospitalized COVID-19 patients with hematologic malignancy had more severe disease and a higher CFR compared to hospitalized healthcare workers. More complications, including acute respiratory distress syndrome, acute kidney failure, and sepsis, were seen in COVID-19 patients with

hematologic malignancy compared with healthcare workers with COVID-19; none of the healthcare providers and eight patients with hematologic malignancy died at the end of observation (P = 0.001) (HE et al. 2020). In a study from Spain, Martin-Moro et al investigated 34 hospitalized COVID-19 patients with hematologic malignancy and observed that the CFR was 32%. They concluded that hematologic malignancy status at the time of COVID-19 is related to mortality; patients without active cancer had better results. 19 In addition, Aries et al. also reported 40% CFR in hemato-oncology patients in their small cohort study including 35 patients (ARIES et al. 2020). In the study by Yang et al among 52 COVID-19 patients with solid tumors or hematologic malignancies, the rate of severe/critical disease was 36.5% and the CFR of severe/critical patients was 57.8% (YANG et al. 2020). In another study, the CFR was 13.8% in COVID-19 patients with hematologic malignancy. The lower CFR in our study compared to the other studies can be attributed to a high number of MPN patients in our study who were considered to be less immunocompromised compared to patients with leukemia, MM or lymphoma. In addition, our study included hospitalized and non-hospitalized patients.

To the best of our knowledge, this is the first large-scale population study that investigates COVID-19 patients with hematologic malignancies and compares its results with an age, sex, and comorbidity-matched cohort of COVID-19 patients without cancer. The main findings of the present study were that (a) hypertension was the most common comorbidity in both groups; (b) rates of serious and critical illness, hospital and ICU admission, and MV support were higher in patients with hematologic malignancy compared with COVID-19 patients without cancer; (c) length of stay and ICU length of stay was similar between groups; (d) CFR was higher in patients with hematologic malignancy compared to the control group;

A retrospective design and lack of information on anticancer treatments and hematologic disease status are limitations of our study. The merits of our study are that the control group was composed of patients matched for age, sex and comorbidity, however, in most studies, control groups are not matched for comorbidity.

DISCUSSION

Our results show that among cancer patients, patients with hematologic malignancies are at higher risk of developing COVID-19 and developing more severe outcomes. It also appears that symptomatic patients also develop worse outcomes than patients who were tested for other reasons.

As found in the Kuderer cohort study, the most frequent type of solid cancer was breast cancer (KUDERER et al. 2020), which is associated with a higher proportion of women included than men. We were unable to examine associations between cancer type and COVID-19 due to the low number of patients in each cancer type. Furthermore, we found no association between lung metastasis and positive RT-PCR for SARS-CoV-2 or severe outcome unlike in other studies (DAI et al. 2020).

We obtained an association with age coming out as a 5% increase in risk of having a positive SARS-CoV-2 RT-PCR each year, which correlates with results found in other publications (KUDERER et al. 2020).

Regarding medical history, we found no association between six chosen comorbidities (hypertension, dyslipidemia, diabetes, thromboembolic disease, chronic obstructive pulmonary disease, COPD) and a positive SARS-CoV-2 RT-PCR test or a serious outcome. This observation extends to

cardiovascular comorbidities, which, although they are the most frequent comorbidities in other studies that include non-cancer patients, did not show a statistically significant association with our dependent variables. This observation contradicts the results found in other studies that included patients without cancer (GUZIK et al. 2020), but mirrors those that include patients with cancer (MENG et al. 2020; YANG et al. 2020). This can be explained by the important impact of cancer itself on the variables studied.

At the beginning of the pandemic, there was limited stock of personal protective equipment (PPE) available and no SARS-CoV-2 PCR swab surveillance on the day of admission for hospitalized patients. We observed four nosocomial infections, one in the hematology unit, one in the palliative care unit, one in the oncology unit and one in our surgical ICU. Additionally, 45% of patients who had contact with a confirmed case were PCR positive for SARS-CoV-2 (compared to 20% PCR positive among patients with compatible symptoms and 10% among patients with compatible imaging). Thereafter, nasopharyngeal swab surveillance was established for each hospitalized patient and caregiver with at least one symptom suggestive of nosocomial COVID-19 infection.

Regarding the nasopharyngeal swab examination indication for COVID-19, 163 patients were tested for COVID-19 symptoms (77%), 29 for incidental imaging findings consistent with COVID-19 (14%), and 20 for contact with a case confirmed (9%). In the same period, 426 patients sought the emergency department for all reasons, 627 patients were hospitalized (and therefore at greater risk of having contact with infected medical staff), and 1,511 patients underwent chest computed tomography (including PET-CT scan). TC). Among patients with RT-PCR positive for SARS-CoV-2, 45% of patients were tested initially because they had close contact with a confirmed case, compared with 20% of patients with compatible symptoms and 10% of patients with imaging compatible with COVID-19. However, 94% of patients with a severe outcome were initially tested for symptoms compatible with COVID-19 and more precisely for respiratory symptoms (cough and desaturation) and/or fever. Among the 16 patients with a severe outcome, 7 were known to have solid tumor (37% of solid tumor patients with PCR positive for SARS-CoV-2) and 8 with hematologic malignancy (57% of hematologic patients with positive SARS -CoV- 2 PCR).

Regarding the correlation between CT and RT-PCR, a total of 197/212 patients underwent the RT-PCR and chest CT test. 61/197 (31%) had a negative RT-PCR test and negative CT findings. 72/197 (37%) had a negative RT-PCR test and atypical CT findings for COVID-19 pneumonia. 46/197 (23%) had a positive RT-PCR test and positive CT findings for COVID-19. However, our data do not allow us to establish a statistical correlation between CT positivity and RT-PCR positivity. This issue is explored, in the same population, in another study (MUKHERJEE et al. 2022).

We highlighted the association with preexisting lymphopenia and hematologic malignancies, which are linked variables, as in our population, 40% of patients with solid tumors had preexisting lymphopenia versus 60% in the hematologic population.

When studying mortality by the severe outcome variable, we defined death related to COVID-19 by separating patients who had worsening symptoms of COVID-19 (22%), from death unrelated to COVID-19 when due to complications associated with cancer (13). %). Indeed, with nosocomial infection in our support ward, and considering the difficulties of organizing outpatient hospital palliative care for COVID-19 positive patients for health

reasons, end-of-life care took place in the COVID-19 unit. In addition, 93% of deceased patients, positive or not for COVID-19, had active limitations of care.

The study has several limitations. First, it is a free literature review study. Second, the study took place months after the COVID-19 pandemic; as a consequence, we do not collect or analyze information about patients' clinical course, rehabilitation and post-COVID 19 syndromes beyond this limited study period.

FINAL CONSIDERATIONS

We confirm that among cancer patients, hematologic malignancies are at higher risk for COVID-19 and develop more severe outcomes, and that hygiene precautions must be introduced as soon as possible during a pandemic.

It is important to consider that patients with hematologic malignancy are immunocompromised, and our study reveals that there is an increased risk of serious events related to COVID-19 (ICU admission, need for MV, or death) in patients with hematologic malignancy compared to patients with cancer-free COVID-19 and supports the high vulnerability of patients with hematologic malignancy in the current pandemic. Therefore, clinicians must pay close attention to the management of COVID-19 patients with hematologic malignancy. Screening performed by telephone or other online technologies must be used to verify the need for treatment or follow-up in outpatient or outpatient clinics. In non-life-threatening illnesses, hospitalization must be postponed.

More studies designed to explore the difference between solid and hematologic patients with larger samples are needed to complete the available data on the impact of intrinsic immunocompromised status and immunosuppressive treatments on seroprevalence, seroconversion, the possibility of reinfection, and immune protection after vaccination. and survival after exposure to SARS-CoV-2.

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