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Original Article

COVID-19-associated pulmonary aspergillosis (CAPA) in hematological patients: Could antifungal prophylaxis be necessary? A nationwide study

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ABSTRACT

Background: COVID-19-associated pulmonary aspergillosis (CAPA) has emerged as a relatively common complication. Multiple studies described this relationship in critical patients, however its incidence and outcome in other risk groups such as immunosuppressed patients remains unknown. In this sense, we aimed to evaluate the rates and outcomes of CAPA in hematological patients and according to the different hematological malignances, comparing to invasive pulmonary aspergillosis (IPA) in non-COVID-19 ones.
Methods: Nationwide, population-based and retrospective observational cohort study including all adult patients with hematological malignancies admitted in Spain since March 1, 2020 to December 31, 2021. The main outcome variable was the diagnosis of IPA during hospitalization in hematological patients with or without COVID-19 at admission. The rate of CAPA compared to IPA in non-COVID-19 patients in each hematological malignancy was also performed, as well as survival curve analysis.
Findings: COVID-19 was diagnosed in 3.85 % (4367 out of 113,525) of the hematological adult inpatients. COVID-19 group developed more fungal infections (5.1 % *vs.* 3 %; $p < 0.001$). Candida spp. showed higher rate in non-COVID-19 (74.2 % *vs.* 66.8 %; $p = 0.015$), meanwhile Aspergillus spp. confirmed its predominance in COVID-19 hematological patients (35.4 % *vs.* 19.1 %; $p < 0.001$). IPA was diagnosed in 703 patients and 11.2 % (79 cases) were CAPA. The multivariate logistic regression analysis found that the diagnosis of COVID-19 disease at hospital admission increased more than two-fold IPA development [OR: 2.5, 95CI (1.9–3.1), $p < 0.001$]. B-cell malignancies – specifically B-cell non-Hodgkin lymphoma, multiple myeloma, chronic lymphocytic leukemia and acute lymphoblastic leukemia – showed between four- and six-fold higher CAPA development and 90-day mortality rates ranging between 50 % and 72 %. However, myeloid malignancies did not show higher CAPA rates compared to IPA in non-COVID-19 patients.

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Conclusion: COVID-19 constitutes an independent risk factor for developing aspergillosis in B-cell hematological malignancies and the use of antifungal prophylaxis during hospitalizations may be warranted.

Introduction

Global statistics, as of the end of December 2023, show that more than 773,000,000 confirmed cases of COVID-19 have been recorded, with nearly 7 million reported deaths [1]. Over time, we have better understood the accurate diagnosis and therapeutic approaches, various clinical manifestations, and their degrees of severity [2–5]. Ultimately, prevention through vaccination is a crucial objective [6]. The clinical course depends on multiple factors, including the SARS-CoV-2 infectious burden [7], comorbidities [8,9], and the development of secondary infections [10]. Concomitant infections are diagnosed in up to 25 % of COVID-19 patients, significantly increasing mortality, with a notable impact on intensive care unit (ICU) patients and oncohematological patients, especially those under active chemotherapy treatment [7,10].

Invasive pulmonary aspergillosis (IPA) can appear within other infectious diseases. Similar to influenza-associated pulmonary aspergillosis [11], COVID-19-associated pulmonary aspergillosis (CAPA) has emerged as a relatively common complication, affecting up to a third of critically ill patients and associated with a mortality rate close to 50 % [12–18]. Damage to the respiratory epithelial lining, either directly by SARS-CoV-2 or as a consequence of the proinflammatory cytokine storm phase, seems to lead to mucociliary clearance dysfunction, facilitating *Aspergillus* spp. spores attachment and subsequent invasion [17,18]. While many studies have included ICU patients, a meta-analysis underscores oncological diseases as a significant host predisposing factor for CAPA [19]. However, the specific type of malignancy was not described.

Since the onset of the COVID-19 pandemic, hematological malignancies have been associated with a more severe infectious course of SARS-CoV-2 infection and worse outcomes [20–26]. This could be explained by the intrinsic immunosuppression linked to the underlying malignancy and the effects of chemotherapy, which result in severe neutropenia and alterations in cellular or humoral immune responses [27]. Therefore, the risk of superinfections also increases [10,28]. Different studies have shown higher rates of bacterial or fungal superinfections in cancer patients. Nosocomial fungal infections have been reported in around 1 % of published series [10,28]. Based on the findings regarding superinfections in critically ill patients, it is likely that the incidence of CAPA also increases in hematological patients [29]. However, the incidence and impact of superinfections – especially CAPA – in COVID-19 patients with hematological malignancies are poorly documented due to the wide heterogeneity of these patients, and very few studies focused in detail on this specific group[10,27,28].

In this regard, the main objective of this study was to evaluate the influence of COVID-19 in the development of associated aspergillosis in hematological patients. The impact of CAPA on patient outcomes was also assessed.

Methods

Study design

A nationwide retrospective population-based study was conducted, including all adult patients (≥18 years old) with hematological malignancies who were admitted to any hospital in Spain from the onset of the COVID-19 pandemic until the latest available national data (from March 1, 2020, to December 31, 2021). The selection criteria and study design are summarized in the flow chart shown in Fig. 1.

Clinical and administrative data were collected from the Spanish Minimum Basic Data Set (MBDS) [30], an administrative database provided by the Ministry of Health. It is estimated to cover 99.5 % of public and private Spanish hospital discharges. This database includes encrypted patient identification numbers, sex, date of birth, hospital outcome, township code, principal and secondary diagnoses, and procedures codes based on the International Classification of Diseases 10th Revision, Clinical Modification (ICD10-CM) [31]. Supplemental Table 1 shows the main ICD10 codes included in the study.

The data were handled with complete confidentiality according to Spanish legislation. This study received approval from the Ethics Committee of Valladolid East Health Area (code PI 22–2855).

Study variables

The main outcome variable was the diagnosis of fungal infection by *Aspergillus* spp. during hospitalization in COVID-19 (called CAPA) and non-COVID-19 (called IPA) hematological patients. COVID-19 patients were represented by those with principal diagnosis at hospital admission.

Infections were categorized into bacterial, viral (excluding COVID-19), and fungal infections. According to etiology, fungal infections were also divided into *Aspergillus* spp., *Candida* spp., and Others. All infections by *Aspergillus* spp. were invasive, associating, at least, lung involvement.

The Spanish Minimum Basic Data Set (MBDS) systematically compiles the classification of infections based on the cultures and microbiological assays conducted utilizing an array of standardized microbiological testing methods. Pathogenic bacteria, viruses, and fungi present in blood, typically sterile bodily fluids, and additional specimens were identified through conventional microbiological techniques upon hospital admission. Confirmation of COVID-19 in hospitalized patients mandatorily necessitated a positive result from a real-time reverse transcription PCR (RT-PCR) test, performed on nasopharyngeal or oropharyngeal swab specimens.

Demographic data included age, sex, comorbidities (diabetes, hypertension, heart disease, chronic renal disease, respiratory disease, neurological disease), length of hospital stay, ICU admission and mortality.

Hematological malignancies

We included the identification of the following hematological malignancies through either a primary or secondary diagnosis at hospital admission: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), T/NK-cell non-Hodgkin lymphoma (T/NK-NHL), Hodgkin lymphoma (HL), B-cell non-Hodgkin lymphoma (B-NHL) and chronic myelomonocytic leukemia (CMML) [32].

Statistical analysis

Descriptive analyses were evaluated using the Chi-square test for categorical variables and the Mann–Whitney U test for continuous

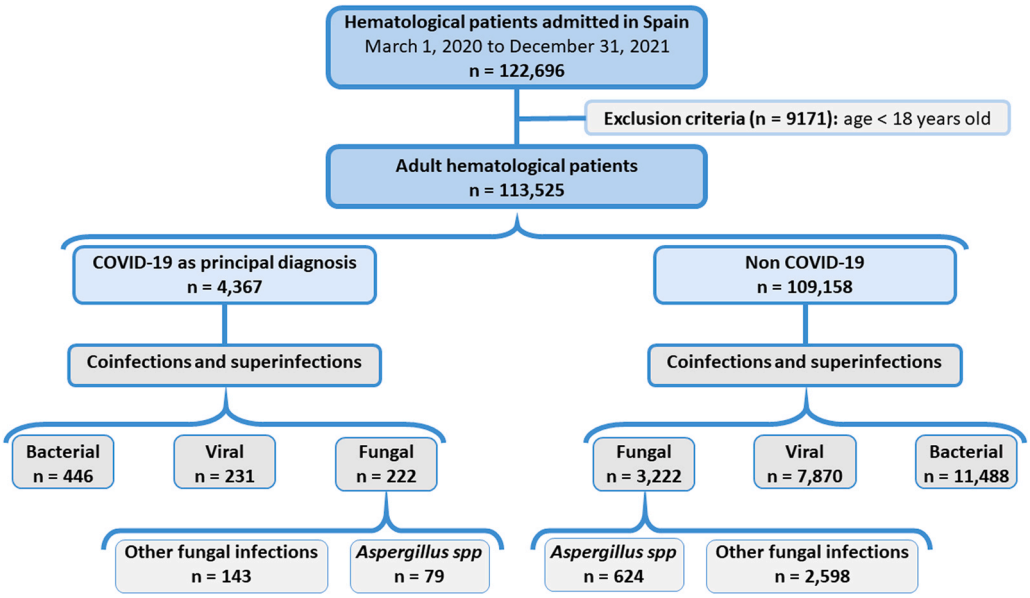

Fig. 1. Flow chart summarizing selection criteria and the study design.

variables. Quantitative variables were described using median values and the interquartile range (IQR), while categorical variables were presented as percentages and total numbers. Clinical characteristics in COVID-19 and non-COVID-19 patients and differences in patients with or without invasive pulmonary aspergillosis (IPA) were described.

The rate of CAPA compared to IPA in non-COVID-19 patients, and according to each hematological malignancy, was also assessed using the Chi-square test and expressed as percentages and total numbers.

Individual logistic regression models, in which the exponential of the coefficients can be directly interpreted as odds ratio, were employed to evaluate the risk of fungal superinfections in COVID-19 hematological patients. In addition, multivariate logistic regression analyses were performed to assess independent associations. Variables related to host predisposing factors for aspergillosis such as comorbidities, age, sex, the presence of COVID-19 or ICU admission were included.

Survival curves were generated to illustrate the 90-day mortality risk evidenced in CAPA, IPA and other fungal infections with or without COVID-19-associated. These curves were created for the entire hematological patient cohort and each subgroup of malignancies. The Kaplan–Meier method and the log-rank test were used.

Descriptive analyses, individual logistic regression models, multivariate logistic regression analyses and survival curves analyses were performed using the R statistical package version 3.1.1 (The R Foundation, Vienna, Austria) and also the statistical package SPSS statistics software (SPSS) version 26 (IBM, Armonk, NY, USA).

Results

A total of 113,525 hematological adult patients were admitted to any hospital in Spain from the onset of the COVID-19 pandemic until the end of 2021. The median age was 66.71 years, with a predominance of males (57.7 %). COVID-19 disease was the primary diagnosis at hospital admission in 3.85 % (4389 patients).

A comparison between COVID-19 and non-COVID-19 hematological patients is presented in Table 1. Hematological COVID-19 patients were significantly older (74 *vs.* 69 years; p < 0.001), predominantly males (59.3 % *vs.* 57.7 %; p = 0.031) and had more comorbidities, including higher rates of diabetes (21.9 % *vs.* 18.5 %; p < 0.001), hypertension (38.5 % *vs.* 32.8 %; p < 0.001), chronic renal disease (8.9 % *vs* 7.5 %; p < 0.001), respiratory disease (17.1 % *vs.* 11.1%; p < 0.001) and neurological diseases (3 % *vs.* 1.9 %; p < 0.001). Bacterial infections were the principal coinfections and superinfections observed in hematological patients, without statistically significant differences between COVID-19 and non-COVID-19 patients (10.2 % *vs.* 10.5 %; p = 0.511). However, patients with COVID-19 at admission developed significantly more fungal infections (5.1 % *vs.* 3 %; p < 0.001), while viral coinfections and superinfections, excluding COVID-19, were more frequent in non-COVID-19 patients (5.3 % *vs.* 7.2 %; p < 0.001). According to fungal etiology, both *Candida* spp. (3.4 % *vs.* 2.2 %; p < 0.001) and *Aspergillus* spp. (1.8 % *vs.* 0.6 %; p < 0.001) increased in COVID-19 compared to non-COVID-19. Thus, CAPA was three-fold more frequent than IPA in non-COVID-19 patients. By cons, other fungal etiologies associated with COVID-19 were exceptional (< 0.1 % *vs.* 0.2 %; p = 0.014) – only one case –, being

Table 1
Comparison of hospitalized adult patients with hematological malignancies according to COVID-19 disease (n = 113,525).

	COVID-19 at admission n = 4367	Non-COVID-19 n = 109,158	*p-value*
Age (years)	74 (19)	69 (21)	**< 0.001**
Sex, male	2590 (59.3 %)	62,949 (57.7 %)	**0.031**
Diabetes	955 (21.9 %)	20,164 (18.5 %)	**< 0.001**
Hypertension	1681 (38.5 %)	35,825 (32.8 %)	**< 0.001**
Heart disease	718 (16.4 %)	17,228 (15.8 %)	0.242
Chronic renal disease	389 (8.9 %)	8165 (7.5 %)	**< 0.001**
Respiratory disease	747 (17.1 %)	12,099 (11.1 %)	**< 0.001**
Neurological disease	129 (3 %)	2068 (1.9 %)	**< 0.001**
Coinfection / Superinfection			
Bacterial	446 (10.2 %)	11,488 (10.5 %)	0.511
Viral	231 (5.3 %)	7870 (7.2 %)	**< 0.001**
Fungal	223 (5.1 %)	3271 (3 %)	**< 0.001**
Fungal etiology			
***Candida* spp.**	149 (3.4 %)	2428 (2.2 %)	**< 0.001**
***Aspergillus* spp.**	79 (1.8 %)	624 (0.6 %)	**< 0.001**
Other spp.	1 (< 0.1 %)	199 (0.2 %)	**0.014**
Hospital meters			
ICU admission	665 (15.2 %)	5600 (5.1 %)	**< 0.001**
Hospital stay (days)	10 (12)	7 (11)	**< 0.001**
In-hospital mortality	1244 (28.5 %)	11,319 (10.4 %)	**< 0.001**

ICU, intensive care unit.

Table 2
Clinical characteristics in hospitalized hematological adult patients according to the presence of IPA (n = 703) during the COVID-19 pandemic.

	IPA n = 703	Non-IPA n = 109,158	*p-value*
Age (years)	64 (20)	69 (22)	**< 0.001**
Sex, male	459 (65.3 %)	65,080 (57.7 %)	**< 0.001**
Diabetes	107 (15.2 %)	21,012 (18.6 %)	**0.021**
Hypertension	178 (25.3 %)	37,328 (33.1 %)	**< 0.001**
Heart disease	91 (12.9 %)	17,855 (15.8 %)	**0.037**
Chronic renal disease	33 (4.7 %)	8521 (7.6 %)	**0.004**
Respiratory disease	121 (17.2 %)	12,725 (11.3 %)	**< 0.001**
Neurological disease	4 (0.6 %)	2193 (1.9 %)	**0.008**
COVID-19 at admission	79 (11.2 %)	4288 (3.8 %)	**< 0.001**
Hospital meters			
ICU admission	180 (25.6 %)	6085 (5.4 %)	**< 0.001**
Hospital stay (days)	25 (30)	7 (11)	**< 0.001**
In-hospital mortality	239 (34 %)	12,324 (10.9 %)	**< 0.001**

IPA, Invasive Pulmonary Aspergillosis; ICU, intensive care unit.

more frequent in non-COVID-19 patients with 199 cases – including 31 cases of mucormycosis and 13 cases of cryptococcosis. Hospitalized COVID-19 patients were admitted more frequently to the ICU (15.2 % *vs.* 5.1 %; p < 0.001), showed a longer hospital stay (10 *vs.* 7 days; p < 0.001), and three-fold higher in-hospital mortality (28.5 % *vs.* 10.4 %; p < 0.001) compared to non-COVID-19 patients.

During this period, fungal infections were diagnosed in 3494 hematological patients during hospitalization. A total of 703 IPA were diagnosed in this period, and 11.2 % (79 cases) were CAPA in hematological patients with COVID-19 at hospital admission. According to the presence of IPA, clinical characteristics in hospitalized hematological adult patients were described in Table 2. IPA group was mainly represented by younger (64 *vs.* 69 years; p < 0.001) males (65.3 % *vs.* 57.7 %; p < 0.001). All comorbidities studied appeared more frequent in the non-IPA group, except respiratory disease, which evidenced higher rates in the IPA group (17.2 % *vs.* 11.3 %; p < 0.001). Moreover, the presence of COVID-19 disease at admission was significantly superior in the IPA compared to the non-IPA group (11.2 % *vs.* 3.8 %; p < 0.001). Hospital meters also showed more ICU admission (25.6 % *vs.* 5.4 %; p < 0.001), hospital stay (30 *vs.* 11 days; p < 0.001), and in-hospital mortality (34 % *vs.* 10.9 %; p < 0.001) in the IPA group.

The multivariate logistic regression analysis presented in Table 3 revealed COVID-19 as an independent risk factor for developing fungal superinfections caused by *Aspergillus* spp. in hospitalized hematological adult patients [OR: 2.455, CI95 % (1.921–3.137), p < 0.001]. SARS-CoV-2 infection increased the risk of aspergillosis by more than two fold, surpassing factors such as sex [OR: 1.302, CI95 % (1.113–1.523), p = 0.001] and significant comorbidities like previous respiratory diseases [OR: 1.673, CI95 % (1.368–2.046), p < 0.001]. ICU admission was the only clinical condition associated with a higher risk of aspergillosis [OR: 5.106, CI95 % (4.280–6.090), p < 0.001] compared to the presence of COVID-19 disease at admission.

Table 3
Multivariate logistic regression analysis to evaluate the independent risk factors associated with developing fungal infection by *Aspergillus* spp. in hematological patients after hospital or ICU admission due to COVID-19 disease.

	Odds Ratio	95 % CI	*p-value*
COVID-19 at admission	**2.455**	**1.921–3.137**	**< 0.001**
Sex, male	1.302	1.113–1.523	**0.001**
Age	0.987	0.982–0.992	**< 0.001**
Diabetes	0.963	0.774–1.197	0.963
Hypertension	0.768	0.640–0.922	**0.005**
Heart disease	0.883	0.700–1.113	0.292
Chronic renal disease	0.698	0.486–1.003	0.052
Respiratory disease	1.673	1.368–2.046	**< 0.001**
Neurological disease	0.434	0.162–1.166	0.098
ICU admission	5.106	4.280–6.090	**< 0.001**

ICU, intensive care unit.

The Kaplan–Meier survival analysis (Fig. 2) stratified into four groups based on mortality risk according to the presence of *Aspergillus* spp. infection and/or COVID-19 disease (Log Rank: p < 0.001). Non-COVID-19 patients exhibited lower 90-day mortality rates compared to COVID-19 patients, reaching a mortality rate of 28.94 % (178/615) in *Aspergillus* spp. infections in comparison to a lower rate in other fungal infections (15.51 %; 403/2598). However, fungal infections during hospitalization in hematological COVID-19 patients were associated with a markedly worse outcome. COVID-19 patients with other fungal infections presented a similar mortality rate to *Aspergillus* spp. infections in non-COVID-19 patients [33.56 % (48/143)]. In contrast, COVID-19-associated invasive aspergillosis showed double mortality rates and reached a 90-day mortality of 66.67 % (52/78).

The subgroup analysis compared the specific rate of IPA in each hematological malignancy according to the presence of COVID-19 (Fig. 3a). Abnormalities related to B lymphocyte – ALL (p = 0.015), CLL (p < 0.001), B-NHL (p < 0.001), and MM (p < 0.001) – showed a statistically significant increased rate of infections by *Aspergillus* spp. in COVID-19 compared to non-COVID-19 patients. Hence, the presence of COVID-19 disease during hospitalization associated between four- and six-fold higher CAPA diagnosis: ALL [OR: 4.5, 95CI (1.1–21.4), p < 0.031], CLL [OR: 3.8, 95CI (2.3–6.3), p < 0.001], B-NHL [OR: 6.6, 95CI (4.5–9.7), p < 0.001] and MM [OR: 5.9, 95CI (3.1–11), p < 0.001]. In contrast, myeloid malignancies – CMML (p = 0.258), CML (p = 0.244) or AML (p = 0.781) –, HL (p = 0.418) and T/NK-NHL (p = 0.450) did not exhibit any differences based on the presence of COVID-19. Moreover, myeloid malignancies had even lower CAPA incidence rates than B-cell neoplasms infected by SARS-CoV-2. Age- and sex-adjusted multivariate logistic regression analysis confirmed the higher risk of CAPA in hematological B-cell neoplasms (ALL, CLL, B-NHL and MM) (Table 4).

According to CAPA diagnosis, the Kaplan–Meier survival subanalysis (Fig. 3b) of each hematological malignancy – including only those with at least 4 events – showed mortality rates greater than 50 %. Specifically, MM presented 6 deaths and 50 % mortality (6 out of 12 patients), and CLL had a higher rate with 68.18 % mortality (15 out of 22 patients). An even higher rate was observed in B-NHL, with a mortality rate of 71.88 % (23 out of 32 patients. Despite the limited number of patients with myeloid malignancies (AML and CMML), they exhibited comparable rates of 75 % and 60 %, respectively, compared to B-cell neoplasms.

Discussion

To our knowledge, this study represents the largest series of patients with hematological malignancies during the COVID-19 pandemic. The main results were: i) The rate of COVID-19 as a primary diagnosis at hospital admission among hematological patients elevated to 3.85 %. ii) COVID-19 emerged as a strong and independent risk factor for developing IPA in hematological patients. iii) B-cell hematological malignancies (B-NHL, CLL, MM, and ALL) exhibited significantly higher risk of CAPA, with 90-day mortality rates ranging between 50 % and 72 %.

Hematological malignancies have been associated with a more severe infectious course of SARS-CoV-2 infection and worse outcomes [20–26]. The rates of COVID-19 in hematological patients have not been clearly described due to the absence of a control group [10,27,28]. Our study matched COVID-19 patients and control group of hematological patients in the same period, establishing 3.85 % of COVID-19 diagnosis in hospitalized hematological patients at hospital admission. Moreover, a clear correlation between the type of hematological neoplasms and the incidence of COVID-19 infection has not been well defined in large series [20–26].

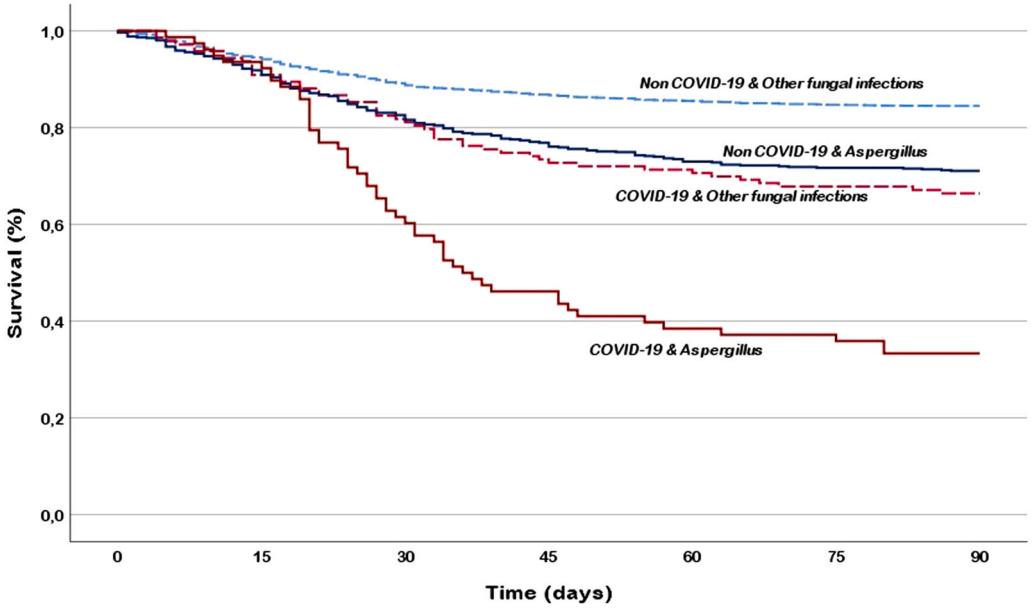

Fig. 2. Kaplan–Meier survival analysis showing the 90-day mortality risk associated with aspergillosis compared to other fungal etiologies in COVID-19 and non-COVID-19 hematological patients. COVID-19 was represented in red, and non-COVID-19 was represented in blue. The continuous line referred to *Aspergillus* spp. and discontinuous to Other fungal infections, respectively.

Bacterial and fungal infections represent significant complications in COVID-19, particularly among hematological patients [10,28]. Nosocomial superinfections appear to be more frequent than coinfections, especially in patients admitted to the ICU and those receiving high doses of corticosteroids [33,34]. Bacterial origin is more common than viral ones [28]. Furthermore, emerging data have demonstrated unexpectedly high rates of fungal infections in critically ill patients with COVID-19, such as candidemia and invasive aspergillosis [17,34]. Our rate of bacterial infections is similar in hematological patients with COVID-19 compared to those without COVID-19, standing at around 10 % in both groups. These results are in line with the incidence evidenced in COVID-19 patients in other studies [10,28]. However, the presence of a control group has allowed us to highlight that there is no increased risk of COVID-19-associated bacterial infections in hematological patients. On the other hand, we evidenced a significant increase in fungal infections, from 3 % in non-COVID-19 patients to 5.1 % in COVID-19 patients, representing a 1.75-fold increased risk.

Regarding invasive aspergillosis, most studies were performed in patients admitted to the ICU and showed varied results. A meta-analysis conducted by Chong *et al.* found 14.9 % of invasive pulmonary aspergillosis in 729 critically ill patients with COVID-19 during the first wave [19]. In contrast, a prospective study conducted by Negm *et al.*, which included 253 COVID-19 patients, showed an overall fungal infection rate of only 3.7 %, rising to 9.6 % in critically ill patients [35]. A systematic review by Krzych *et al.* stated that aspergillosis was the most frequently described fungal infection in COVID-19 (approximately 1 in 10 patients), followed by candidiasis (approximately 1 in 33 patients) [7].

Studies in hematological patients are very limited, often lacking a control group of non-COVID-19 patients, and they are not primarily designed to evaluate the incidence of fungal infections and invasive aspergillosis associated with COVID-19 [24]. García-Vidal *et al.* reported a 0.7 % rate (7 out of 989 patients) of fungal hospital-acquired superinfections, with four cases attributed to *Candida* spp. and three cases to *Aspergillus* spp.. However, these cases were related to tracheobronchitis caused by *Aspergillus* spp., with no cases of invasive fungal infection (IFI) [10]. Gudiol *et al.* presented only one case of documented IFI, although three patients were also diagnosed with tracheobronchitis by *Aspergillus* spp. [28]. Zappasodi *et al.* evidenced 18 fungal infections, comprising 9.7 % of their cases. These infections were mainly caused by yeasts (61.1 %), all of which were IFI, with 7 probable aspergillosis cases (38.9 %) and 11 proven candidemias (61.1 %) [27]. These results align with our findings, identifying 223 fungal infections (5.1 %) and 79 proven cases of proven CAPA (1.8 %). When comparing these various studies in hematological and immunocompetent critical patients, the lower rate of proven invasive aspergillosis in hematological patients may be attributed to the reduced availability of direct microbiological cultures, such as bronchoalveolar lavage (BAL), and their lower yield in hematological patients [36,37]. The presence of a control group and the large sample size in our study have confirmed that SARS-CoV-2 is a fundamental risk factor for fungal superinfection, especially in elderly patients with pre-existing respiratory disease. This risk is only surpassed by ICU admission. Until now, this relationship has not been directly demonstrated in hematological patients with COVID-19.

Moreover, our extensive sample size enabled the inclusion of 79 cases of CAPA in hematological patients and facilitated a subgroup analysis. Consequently, we observed a significantly higher incidence of CAPA in patients with B-cell hematological neoplasms, while no such differences were noted in myeloid neoplasms. Several factors, including poor vaccine response [38–40], humoral immunity alterations, intrinsic immunosuppression, and the widespread use of high-dose corticosteroids, seem to contribute to the susceptibility to invasive aspergillosis [7,37].

The American and European guidelines for primary antifungal prophylaxis in adult hematology patients recommend the use of oral triazole antifungal prophylaxis in AML, high-risk MDS, and special situations that increase the risk of IFI, such as prolonged periods of neutropenia or the use of long-term corticosteroids [36,37]. Based on our results, we observed that CAPA preferably occurred in B-cell hematological neoplasms. It means that it equals or surpasses the associated risk of IFI in myeloid neoplasms, regardless of COVID-19. Therefore, considering the guideline recommendations, it may be advisable to contemplate using prophylactic triazoles during hospitalization of hematological patients with B-cell hematological neoplasms (ALL, MM, B-NHL, and CLL).

Nevertheless, the recent escalation in triazole resistance among *Aspergillus* spp. warrants consideration. Although this trait currently exhibits a low incidence and demonstrates considerable variability

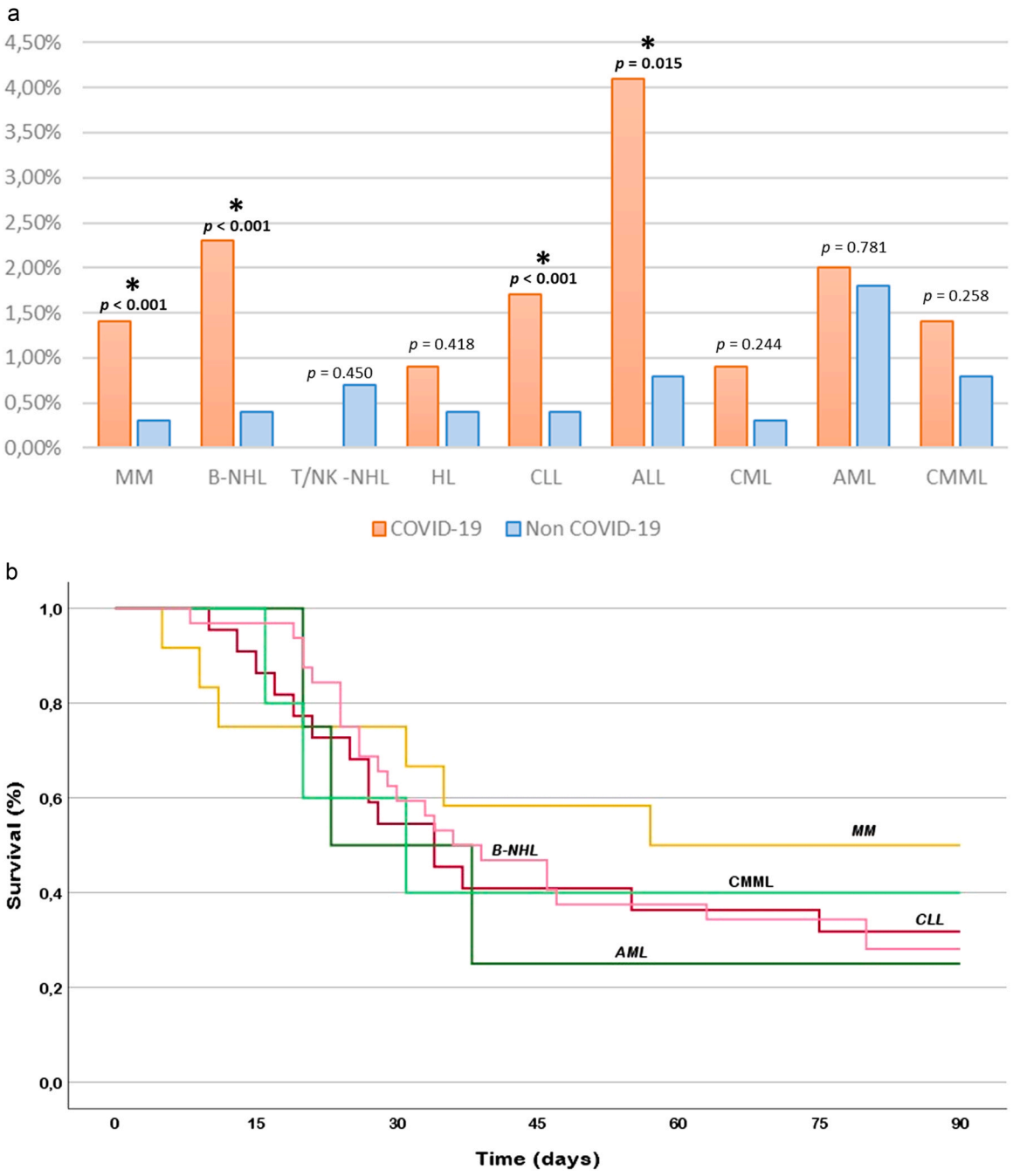

Fig. 3. a) Rate of aspergillosis in hematological malignancies comparing COVID-19 and non-COVID-19 patients. b) Kaplan–Meier survival analysis showing the 90-day mortality risk associated with CAPA in MM, CMML, CLL, B-NHL, and AML. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; T/NK-NHL, T/NK-cell non-Hodgkin lymphoma; HL, Hodgkin lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; CMML, chronic myelomonocytic leukemia; MM, multiple myeloma.

Table 4
Sex- and age-adjusted multivariate logistic regression analysis to evaluate the independent association of COVID-19 disease and the risk of fungal infection by *Aspergillus* in B-NHL, MM, CLL and ALL.

	Odds Ratio	95 % CI	*p-value*
B-NHL	6.611	4.491–9.732	**< 0.001**
MM	5.861	3.125–10.990	**< 0.001**
CLL	3.823	2.314–6.318	**< 0.001**
ALL	4.968	1.154–21.398	**0.031**

B-NHL, B-cell non-Hodgkin lymphoma; MM, multiple myeloma; CLL, chronic lymphocytic leukemia; ALL, acute lymphoblastic leukemia.

across diverse geographical areas, an in-depth understanding of this resistance pattern is crucial to refine and optimize antifungal prophylaxis and therapeutic strategies.

The high incidence of COVID-19-associated invasive aspergillosis was accompanied by a severe 90-day mortality rate that reached 66.67 % among all hematological patients. B-cell hematological malignancies (B-NHL, CLL, MM, and ALL) exhibited 90-day mortality rates ranging from 50 % to 72 %. These mortality rates were similar to published data for critically ill or oncological patients [15–17,19]. Once again, these findings highlight the potential benefits of antifungal prophylaxis in such cases. This evidence strongly supports the

need for prospective multicenter studies, given that COVID-19 is expected to persist as a common and sometimes severe viral infection among immunosuppressed patients, including those with hematological conditions.

The strengths of this nationwide study are underscored by the substantial cohort of patients included, with up to 4367 hematological patients as well as the comprehensive and complete collection of clinical and microbiological data. Furthermore, the direct comparison between hematological COVID-19 and non-COVID-19 patients was outstanding. However, it is essential to acknowledge some significant limitations. Firstly, this is a retrospective study based on a national database. Secondly, the classification of etiology is based on microbiological culture positivity. Thirdly, the low yield of cultures in hematological patients may limit the study and potentially underestimate the incidence. Additionally, data on possible/probable invasive aspergillosis are unavailable. Finally, information about specific characteristics of each hematological disease, such as the type of treatment, prior lines of therapy, or the degree of neutropenia, was unavailable.

Conclusions

In conclusion, this study has demonstrated that COVID-19 constitutes an independent risk factor for developing aspergillosis in hematological patients during hospitalization. Specifically, individuals with B-cell hematological malignancies (B-NHL, CLL, MM, and ALL) exhibited an elevated risk of CAPA, which is even higher than IPA risk in AML patients. It resulted in 90-day mortality rates ranging from 50 % to 72 %. These findings open the possibility of conducting prospective studies and clinical trials to assess the potential advantages of antifungal prophylaxis during hospitalization in individuals with B-cell hematological malignancies with COVID-19 disease at admission.

Ethical approval

The study protocol was approved by the Ethics Committee for Clinical Research, Hospital Clinico Universitario in Valladolid, Spain (approval No. PI 22–2855). This study followed current Spanish legislation for biomedical research, fulfilling the standards indicated by the Declaration of Helsinki.

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CRediT authorship contribution statement

Conceptualization: ATV, MJPP, JPMG. Resources: ATV, AAM, SR, ET. Formal analysis: ATV, MMF, AAM. Investigation: ATV, RLH, LMGG, GAM, MBC. Methodology: ATV, RLH, LSdP, SR, MJPP. Supervision: ET, SR, JPMG, MJPP. Visualization: ATV, RLH, GAM, AAM. Writing-original draft: ATV, RLH, LMGG, GAM, LSdP, MBC. Writing-review and editing: ATV, MMF, AAM, ET, SR, JPMG, MJPP. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2024.04.005.

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