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Hospital-treated serious and invasive aspergillosis and candidiasis infections during the COVID-19 pandemic: a retrospective analysis of Hospital Episode Statistics data from England

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ABSTRACT

Objectives To investigate the impact of COVID-19 on the burden of hospital-treated *Aspergillus* and *Candida* infections in England.

Design A retrospective study using Hospital Episodes Statistics data to estimate the burden of serious and invasive fungal infections (SIFIs) in all patients admitted in England during March 2018–February 2020 (pre-COVID-19) and during March 2020–October 2021 (the COVID-19 period).

Setting Hospitals in England.

Population All patients with codes corresponding to serious and invasive aspergillosis and candidiasis in any diagnosis position during their admission pre-COVID-19 and during the COVID-19 period.

Outcome measures Age, spells, patient counts, mean length of stay, admission to critical care unit (CCU), length of stay in CCU, 30-day readmissions, failed discharges (readmission within 7 days) and comorbidities.

Results During the COVID-19 period, hospitalisation spells with an invasive candidiasis code fell by 3.2% and spells with an aspergillosis code by 24.8%. Mean length of stay was higher for patients with aspergillosis with or without COVID-19 and candidiasis with or without COVID-19 during the pandemic than before the pandemic. During the pandemic, mean length of stay was higher for patients with aspergillosis with COVID-19 than those with aspergillosis alone but slightly lower for patients with candidiasis with COVID-19 than for those with candidiasis alone. Of patients with a diagnosis of COVID-19, 52.5% with aspergillosis and 60.0% with candidiasis were treated in CCU compared with 13.2% and 37.1%, respectively, without a COVID-19 diagnosis. The percentage of 30-day readmissions and failed discharges for patients with SIFI was higher for those with COVID-19 than for those without.

Conclusions The burden of aspergillosis and candidiasis has been affected by COVID-19. Aspergillosis diagnoses fell among hospitalised patients during the pandemic, while candidiasis continued to fluctuate in patterns similar to pre-COVID-19. A higher burden for patients with SIFI was observed, whether or not they also had a diagnosis of COVID-19. Our findings highlight extra considerations and burden on management of serious SIFI as a result of the COVID-19 pandemic.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This analysis used recent real-world data from the Hospital Episodes Statistics (HES) dataset, which includes all patients using secondary care services in England.
⇒ The data are coded based on information documented within medical records and are, therefore, dependent on the quality of the coding.
⇒ Accuracy of diagnosis of fungal infections is recognised as a clinical and coding issue.
⇒ The codes used were carefully considered to minimise inclusion of any non-severe fungal infections, such as topical *Candida* infections; the results are, therefore, likely to underreport candidal infections.
⇒ Data on final destination and all mortality are not available from HES, which can impact on understanding of patient outcomes.

INTRODUCTION

In recent years, global health awareness around infectious diseases has increased. However, the profile of fungal infections has lagged behind that of bacterial and viral diseases, despite serious and invasive fungal infections (SIFIs) often resulting in poorer patient outcomes, more complexity and increased burden on healthcare systems.

Invasive fungal infections

Invasive aspergillosis

Aspergillus is a ubiquitous environmental mould that grows on organic matter.[1–3] It produces aerosolised conidia, which can be inhaled by humans, potentially leading to colonisation and infection, primarily in immunocompromised individuals.[1] *Aspergillus* causes a spectrum of pulmonary

disorders and clinical manifestations, depending on the competence of the host's immune response, including local colonisation of the respiratory tract, hypersensitivity reactions, chronic infections and acutely invasive disease.[1–4] Aspergillosis is a significant cause of morbidity and mortality in the immunocompromised population.[4] Invasive aspergillosis (IA) is characterised by invasion of pulmonary vasculature by the *Aspergillus* hyphae, which can progress to angioinvasive pulmonary aspergillosis.[1 2] IA and angioinvasive pulmonary aspergillosis are serious conditions that can complicate the management of critically ill patients, with up to 95% mortality if not treated.[1 4]

Invasive candidiasis

Candida is a widespread genus of commensal yeasts that can be detected on the mucosal surfaces (skin and gut) of healthy humans and in the hospital environment.[1 5] They are typically non-pathogenic in immunocompetent people, but at least 15 *Candida* species can cause human disease.[1 5–7]

As with *Aspergillus*, *Candida* are implicated in a broad spectrum of infections, with candidiasis an umbrella term covering cutaneous, mucosal and deep-seated organ infections.[7] Invasive disease results from a combination of increased or abnormal colonisation, disruptions in the cutaneous and gastrointestinal barriers, and local or general defects in host defences, including weakened immunity.[7] More than 95% of invasive disease is caused by six species, most commonly *Candida albicans* and increasingly *C. auris and C. glabrata*.[5–7] Invasive candidiasis can range from minimally symptomatic candidaemia to deep-seated infection with or without candidaemia, including fulminant sepsis, which has >70% mortality.[7] Surveillance data from the UK in 2020 show the highest rate of candidaemia observed in the past 10 years at 3.5 per 100 000 population.[8]

Impact of COVID-19

The COVID-19 pandemic has presented many challenges to healthcare systems, including the emergence of associated and secondary infections, especially in severe cases treated in the intensive care unit.[1] COVID-19 infection leads to conditions favourable for opportunistic fungal pathogens, such as hypoxia, immunosuppression, host iron depletion, hyperglycaemia secondary to diabetes and prolonged hospitalisation, even in previously immunocompetent people.[9] The prevalence of COVID-19-associated pulmonary aspergillosis (CAPA) varies. A national French study reported rates of 15% in mechanically ventilated patients and higher mortality in patients with CAPA than in those without (61.8% vs 32.1%).[10] A small number of studies from outside of the UK has identified extrapulmonary mould infections in patients with COVID-19, including disseminated aspergillosis (pulmonary and cerebral) and rhinosinusitis.[11 12]

The risk of candidiasis may also significantly increase in patients with severe COVID-19 due to treatment with broad-spectrum antibacterials, parenteral nutrition, invasive examinations, prolonged neutropenia and other immune impairment.[13] COVID-19-associated candidiasis has been reported in 0.7%–23.5% of patients with severe infection and with mortality of 83.3%.[9 10] Candidal infections of the bloodstream and abdomen in patients with COVID-19, most frequently *C. albicans* but also other species, including *C. auris*, have also been reported worldwide, including the UK.[14]

Any variation in incidence of fungal infections could lead to a significant change in the burden on healthcare systems.[15] Even before the COVID-19 pandemic, invasive fungal disease was thought to be increasing in the UK due to a variety of factors, including increased survival time from previously fatal illnesses and an increase in immunosuppression from the treatment of other diseases.[15] Comorbid COVID-19 and fungal infections will have further added to the burden on healthcare systems and critical care services during the pandemic.

Understanding of the overall burden of invasive fungal disease in the UK is limited, as active surveillance is in place only for candidaemia, and even then the burden is likely to be underestimated as reporting of candidaemia by laboratories has been voluntary.[15] We, therefore, investigated the impact of COVID-19 on the reported disease burden of serious and invasive *Aspergillus* and *Candida* infections in hospitals in England.

PATIENTS AND METHODS

We used Hospital Episodes Statistics (HES) data to estimate the burden of serious aspergillosis, IA and candidiasis infections in all patients admitted in England pre-COVID-19 (March 2018–February 2020) and during March 2020–October 2021 (the COVID-19 period). During the COVID-19 period, we estimated the burden of serious aspergillosis, IA and candidiasis infections in patients with and without a diagnosis code for COVID-19. We initially identified patients with all diagnosis codes corresponding to aspergillosis and candidiasis in any diagnosis position during their admission (ie, as primary diagnosis or secondary diagnosis) pre-COVID-19 and during the COVID-19 period. The codes for candidiasis initially included B37.8 (candidiasis of other sites—*Candida*; cheilitis and enteritis) and B37.9 (candidiasis, unspecified—thrush not otherwise specified); however, these were later removed from the analysis so as to minimise inclusion of any non-severe fungal infections, such as topical *Candida* infections. Details on coding used are given in online supplemental appendix A and online supplemental tables A and B. Throughout the rest of this paper, 'candidiasis' refers to serious and invasive candidiasis and 'aspergillosis' refers to IA. The analysis is based on the date of discharge—that is, the month in which the patient was discharged from hospital is the month in which the admission is counted. Only patients registered at a general practice in England at the time of admission have been included in the study.

Specific characteristics of interest included age, spells, patient counts, mean length of stay (MLOS), admission to critical care unit (CCU), length of stay in CCU, 30-day readmissions, failed discharges (readmission within 7 days) and comorbidities. Patient counts refer to the number of unique patients who have been admitted to hospital with a diagnosis of interest in the specified time period (using person identifier in HES). Spell counts refer to the total number of admissions to hospital where a patient has been coded with a diagnosis of interest over the specified time period (using spell identifier in HES). A unique patient may have more than one hospital spell over a given time period but will only be counted once in patient counts. MLOS was defined as total bed-days in a spell divided by the number of spells with a SIFI diagnosis. Thirty-day readmissions were defined as a non-elective admission with a diagnosis of SIFI that was within 30 days of a discharge for a spell where the patient also had SIFI. Failed discharges were defined as non-elective admissions with a diagnosis of SIFI within 7 days of a discharge for a spell where the patient also had SIFI. We identified the top 15 most common comorbidities in SIFI spells during the pre-COVID-19 period and the top 15 most common comorbidities in SIFI spells during the COVID-19 period.

As required by NHS Digital when using HES data, values for patients, spells, patients in critical care, spells in critical care, critical care days, 30-day readmissions and count of failed discharges above 7 were rounded to the nearest 5; totals, therefore, may not sum across columns/rows. Values for patients, spells, patients in critical care, spells in critical care, critical care days, 30-day readmissions and count of failed discharges between 1 and 7 (inclusive) were suppressed for data presented at an aggregated level. MLOS was suppressed where spells were suppressed.

Secondary care data are taken from the English HES database produced by NHS Digital, the new trading name for the Health and Social Care Information Centre (HSCIC). Copyright 2023, the Health and Social Care Information Centre. Re-used with the permission of the Health and Social Care Information Centre. All rights reserved. Access to licenced HES data provided through Wilmington Healthcare. See online supplemental appendix B for full HES disclaimer.

Patient and public involvement

Patients and/or the public were not involved in this study.

RESULTS

Population

During the period before COVID-19 (March 2018–February 2020), 6255 patients had aspergillosis and 3445 had candidiasis. Of the patients with SIFI during the COVID-19 period (March 2020–October 2021), 4350 with aspergillosis and 2385 with candidiasis had no previous diagnosis of COVID-19, while 600 with either infection had a diagnosis of COVID-19.

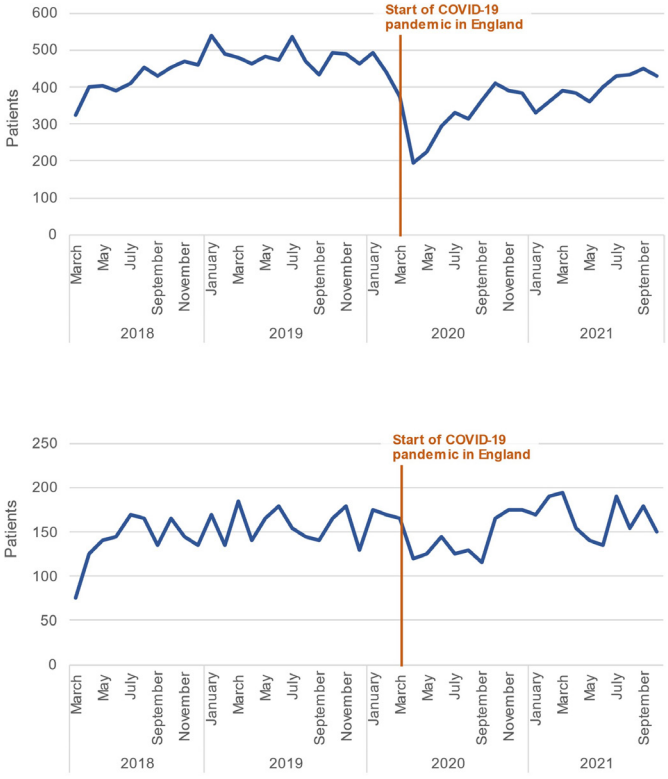

Figure 1 Monthly trends in aspergillosis (A) and candidiasis (B) patient count before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020–October 2021).

Monthly patient counts are shown in figure 1.

Hospitalisation spells with a candidiasis code fell by 3.2% over the entire COVID-19 period compared with before COVID-19 and spells with an aspergillosis code fell by 24.8%.

Distribution of aspergillosis across patients younger than 65 years and older than 65 years remained similar prior to and during the pandemic, with comparable decreases at the beginning of the pandemic for the two age groups and a slow recovery to pre-COVID-19 baseline levels (online supplemental figure A). Monthly counts of candidiasis in both age groups were broadly similar throughout the study period. However, although a trend for higher counts of candidiasis was observed among patients older than 65 years compared with those younger than 65 years before the pandemic, counts in the younger age group were higher than in the older age group at points during the pandemic (see online supplemental figure A).

MLOS and readmissions

MLOS was higher during the pandemic than before the pandemic for patients with aspergillosis with and without COVID-19 (10.2 days during pandemic vs 7.7 days before pandemic) and for patients with candidiasis with and without COVID-19 (28.6 days during pandemic vs 23.3 days before pandemic) (see figure 2; online supplemental table B). During the pandemic, MLOS was higher for

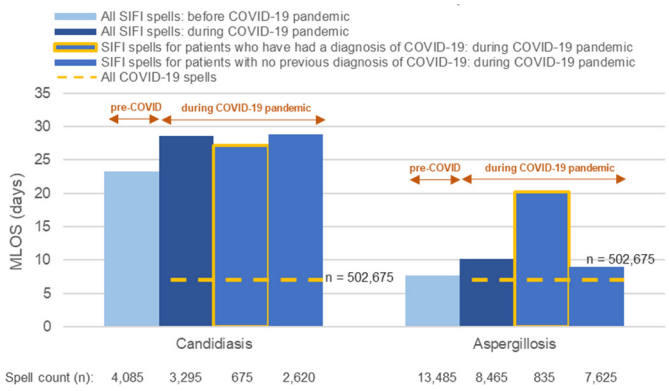

Figure 2 MLOS for spells with SIFI and/or COVID-19 spells before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021). MLOS, mean length of stay; SIFI, serious and invasive fungal infection.

patients with aspergillosis and COVID-19 than those with aspergillosis alone (20.2 days vs 9.0 days, respectively) but slightly lower for patients with candidiasis and COVID-19 than for those with candidiasis alone (27.2 days vs 28.8 days, respectively).

The percentage of 30-day readmissions for patients with SIFI was higher for those with COVID-19 than for those without COVID-19: 12.6% versus 8.6% for patients with aspergillosis and 3.7% versus 2.5% for those with candidiasis (figure 3). A similar trend was seen for rates of failed discharge for those with COVID-19 and those without COVID-19: 7% versus 4%, respectively, for patients with aspergillosis and 3% versus 2%, respectively, for patients with candidiasis (figure 3).

Admission to critical care and length of stay

Of the patients with a previous diagnosis of COVID-19, 52.5% with aspergillosis and 60.0% with candidiasis were treated in CCU. In comparison, of the patients with no previous diagnosis of COVID-19, 13.2% with aspergillosis and 37.1% with candidiasis were treated in CCU (online supplemental table B).

MLOS in CCU for patients without COVID-19 was 18.1 days for patients with aspergillosis and 22 days for

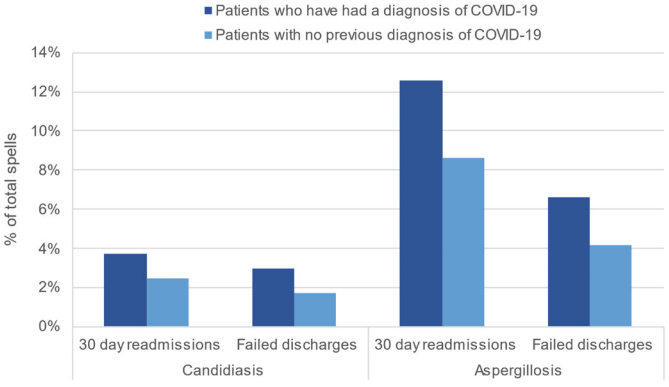

Figure 3 Readmissions within 30 days and failed discharges for patients with aspergillosis and candidiasis during the COVID-19 period (March 2020–October 2021).

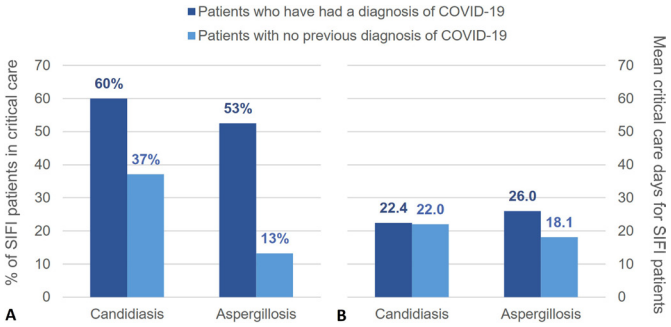

Figure 4 Patients admitted to critical care (A) and MLOS in critical care (B) for spells with aspergillosis and candidiasis during the COVID-19 period (March 2020–October 2021). MLOS, mean length of stay; SIFI, serious and invasive fungal infection.

those with candidiasis; this increased to 26 days and 22.4 days, respectively, for patients who also had COVID-19 (figure 4).

Comorbidities

For patients with aspergillosis, four codes not in the top 15 comorbidities prior to COVID-19 were ranked in the top 15 during the COVID-19 period: special screening examination for other viral diseases, other physical therapy, personal history of long-term (current) use of anticoagulants and acute renal failure, unspecified (table 1).

For patients with candidiasis, five codes not in the top 15 comorbidities prior to COVID-19 were ranked in the top 15 during the COVID-19 period: COVID-19, virus identified; other viral pneumonia; COVID-19 as the cause of diseases classified to other chapters; respiratory failure, unspecified—type I (hypoxic); and special screening examination for other viral diseases (table 1).

DISCUSSION

Overall hospital admissions decreased at the start of the COVID-19 pandemic. This effect was mirrored in the number of aspergillosis diagnoses, with pre-COVID-19 pandemic levels of aspergillosis coding only returning after 12 months. However, this did not apply to candidiasis, where a slight decrease was observed but not to the extent observed with aspergillosis.

Our data suggest that IA is more frequent than invasive candidiasis, whereas candidiasis is more common in clinical practice.[15 16] We only included codes specific to invasive infection in our study—for example, we excluded code B37.9 'candidiasis, unspecified', which is applicable to 'thrush not otherwise specified', a non-invasive form of candidiasis. Consequently, cases of invasive *Candida* infection that were miscoded as non-invasive forms would have been excluded from our analysis, resulting in an apparently lower rate for invasive candidiasis. MLOS for candidiasis in our analysis was longer than for aspergillosis. Other studies have shown variation in this, with some demonstrating longer lengths of stay for aspergillosis while others aligned with our findings.[17–19]

Table 1 Top 15 most common comorbidities (ordered by rank during the COVID-19 period) in hospital spells of patients with aspergillosis or candidiasis before COVID-19 (March 2018–February 2020) and during the COVID-19 period (March 2020 to October 2021)

	Aspergillosis				Candidiasis			
			Occurrence (%)				Occurrence (%)	
Rank during COVID-19 period	Rank before COVID-19	ICD-10 code Diagnosis description	Before COVID-19	During COVID-19	Rank before COVID-19	ICD-10 code Diagnosis description	Before COVID-19	During COVID-19
1	1	J99.8 Respiratory disorders in other diseases classified elsewhere	52.6	51.1	2	N17.9 Acute renal failure, unspecified	24.1	34.0
2	2	J47.X Bronchiectasis	32.0	30.8	1	I10.X Essential (primary) hypertension	33.7	32.0
3	3	I10.X Essential (primary) hypertension	21.8	25.1	4	J17.2 Pneumonia in mycoses	18.1	20.6
4	5	Z86.4 Personal history of psychoactive substance abuse	19.7	19.8	–	U07.1 COVID-19, virus identified	Not ranked in top 15	20.0
5	4	J45.9 Asthma, unspecified	20.2	19.7	5	J90.X Pleural effusion, not elsewhere classified	14.5	18.7
6	–	Z11.5 Special screening examination for other viral diseases	Not ranked in top 15	16.1	–	J12.8 Other viral pneumonia	Not ranked in top 15	18.1
7	–	Z50.1 Other physical therapy	Not ranked in top 15	12.3	–	B97.2 Coronavirus as the cause of diseases classified to other chapters	Not ranked in top 15	17.8
8	9	Z86.7 Personal history of diseases of the circulatory system	10.3	12.2	13	Z50.1 Other physical therapy	11.6	17.7
9	8	Z86.1 Personal history of infectious and parasitic diseases	11.0	12.1	3	J99.8 Respiratory disorders in other diseases classified elsewhere	19.0	17.4
10	6	J44.0 COPD with acute lower respiratory infection	11.9	11.9	6*	E11.9 T2DM—without complications	13.9	17.0
11	7	J44.9 COPD, unspecified	11.7	11.8	15	Y95.X Nosocomial condition	10.7	14.5
12	11	J43.9 Emphysema, unspecified	9.9	11.2	10	I48.9 Atrial fibrillation and atrial flutter, unspecified	12.6	13.4
13	10	E11.9 T2DM—without complications	10.0	11.0	–	J969.0 Respiratory failure, unspecified—type I (hypoxic)	Not ranked in top 15	13.0

Continued

Table 1 Continued

Rank during COVID-19 period	Aspergillosis					Candidiasis				
	Rank before COVID-19	ICD-10 code Diagnosis description	Occurrence (%)			Rank before COVID-19	ICD-10 code Diagnosis description	Occurrence (%)		
			Before COVID-19	During COVID-19				Before COVID-19	During COVID-19	
14	–	Z92.1 Personal history of long-term (current) use of anticoagulants	Not ranked in top 15	10.2		–	Z11.5 Special screening examination for other viral diseases	Not ranked in top 15	13.0	
15	–	N17.9 Acute renal failure, unspecified	Not ranked in top 15	9.7		11	J18.1 Lobar pneumonia, unspecified	12.6	12.9	

The shaded cells highlight the comorbidities not ranked in top 15.
*Formerly coded as 'emergency use of U07.1', updated to 'COVID-19, virus identified'.
COPD, chronic obstructive pulmonary disease; ICD-10, International Classification of Diseases and Related Health Problems 10th revision; T2DM, type 2 diabetes mellitus.

The pattern of monthly counts for patients admitted with aspergillosis who were younger or older than 65 years was broadly similar; however, prolonged divergence was seen for patients with candidiasis during the first wave of the pandemic. Fewer bronchoscopies and necropsies were performed during the pandemic, especially in the first months, due to the risks of aerosol generation,[20–22] which may have resulted in an apparent reduction in the occurrence of IA during the pandemic due to reduced diagnoses, although the actual number of infections may not have reduced. Conversely, some cases of *Aspergillus* spp colonisation may have been incorrectly interpreted as IA as the classification and severity of aspergillosis—for example, devised by Koehler *et al* for CAPA[23]—is not available from the HES data.

Of note, the number of cases of candidiasis was higher in those younger than 65 years compared with those older than 65 years at some points during the pandemic, generally corresponding with national lockdowns, which is a reversal of the typical trend prior to the pandemic. The reason for this is uncertain, but it may relate to the fact that older patients were at much higher risk of mortality from COVID-19,[24] which may have impacted the prevalence of secondary infections such as candidiasis. Surprisingly, despite this divergence between the age groups, with fewer patients older than 65 years diagnosed with serious and invasive candidiasis than those younger than 65 years, the overall number of patients diagnosed with candidiasis during the pandemic actually increased compared with pre-pandemic (+3.8%).

Attempting to establish the burden of SIFI during the pandemic is complex, but there is clear evidence of an increase in the number of days patients spent in hospital, the care required and the complexities experienced. This includes increased renal disorders such as acute kidney injury, which is one of the most frequent organ complications in patients with severe COVID-19,[25] with studies indicating >30% of patients hospitalised with COVID-19 develop kidney injury and >50% of patients in CCU with kidney injury may require dialysis.[26] Accordingly, our analysis saw acute renal failure appear in the top 15 comorbidities for patients with aspergillosis and increase from rank 2 to rank 1 for those with candidiasis. Coagulopathies have been associated with COVID-19 in patients with aspergillosis,[27] and personal history of long-term (current) anticoagulants emerged in the top 15 comorbidities in patients with aspergillosis during the COVID-19 period in our analysis. Further investigation to identify any correlation between preidentified comorbidities and subsequent development of serious aspergillosis and IA and candidiasis during the COVID-19 pandemic may provide further insight.

During the pandemic, patients with aspergillosis or candidiasis who also had a COVID-19 diagnosis code, with some exceptions, showed increased disease burden and worse outcomes compared with patients with aspergillosis or candidiasis without a COVID-19 diagnosis code. This included increases in admission rates to CCU,

CCU MLOS, 30-day readmissions and failed discharges. Patients with codes for aspergillosis or candidiasis with a COVID-19 diagnosis in the readmission spell or in any previous spell had higher readmission rates than those with no record of a COVID-19 diagnosis in the readmission or any previous spell. This increase in readmission rates could be because of their combined history of COVID-19 along with SIFI suggesting a worse prognosis and more complicated disease course than for those SIFI patients who have never had COVID-19. Patients with codes for aspergillosis plus COVID-19 also showed increases in overall MLOS and MLOS in CCU compared with patients with COVID-19 alone. Notably, during the pandemic, patients with codes for candidiasis and COVID-19 had shorter lengths of stay than those with candidiasis alone (see figure 2).

During the pandemic, increased use of codes for viral screening; COVID-19; COVID-19, virus identified; and respiratory comorbidities would be expected (see table 1). The appearance of other physical therapy, renal failure (a known complication of COVID-19) and increased use of oral anticoagulants for patients with aspergillosis is unsurprising, as renal tropism and coagulopathies are known to develop in patients with COVID-19, as well as a requirement for rehabilitation;[25 26 28–36] however, it is notable that these appeared in the top 15 codes for aspergillosis but not for candidiasis.

Strengths and limitations

This analysis used recent real-world data from the HES dataset, which includes all patients using secondary care services in England.

The data were coded based on information documented within the medical records and are, therefore, dependent on the quality of the coding, including the accuracy of diagnosis of fungal infections. Excluding codes B37.8 (candidiasis of other sites—*Candida* cheilitis and enteritis) and B37.9 (candidiasis, unspecified—thrush not otherwise specified) to minimise inclusion of any non-severe fungal infections, such as topical *Candida* infections, means that the results presented are likely to underreport infections, with some cases of invasive candidiasis and candidaemia missed. Data on final destination and all mortality are not available from HES, which can have an impact on understanding of patient outcomes. Patients not registered at a general practice in England at the time of admission were not included and so diagnoses may be underestimated.

CONCLUSIONS

The burden of aspergillosis and of candidiasis has been affected by COVID-19. While diagnoses of aspergillosis fell among hospitalised patients during the pandemic, candidiasis continued to fluctuate in patterns similar to before COVID. However, a higher burden for patients with SIFI was observed, irrespective of whether or not they also had a diagnosis of COVID-19. Compared with patients with SIFI or COVID-19 alone, patients with both codes had increased CCU admissions and longer CCU MLOS, as well as higher 30-day readmission and failed discharge rates. The amplified care needs of patients with both codes suggests complexity in care that increased the disease burden of SIFIs on the English healthcare system. Our findings highlight the extra considerations and burden on management of serious SIFI as a result of the COVID-19 pandemic, not only in England but countries globally. Further work is required to fully understand the impact of the COVID-19 on hospital-treated SIFIs.

Contributors MS, AHS, JKS and ST contributed to the idea of the study and protocol development. ST performed the data analysis. JKS and JL drafted the manuscript. All authors reviewed all drafts of the manuscript and approved the final version for submission. GK is guarantor for the study.

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Competing interests The study was funded by Pfizer and conducted by Wilmington Healthcare. AHS is an employee of Pfizer and holds stock or stock options in Pfizer. MS and GK are employees of Pfizer and hold stock or stock options in Pfizer. JKS and ST are employees of Wilmington Healthcare. JL received funding provided by Pfizer through Wilmington Healthcare for medical writing.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

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