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## Is there an association between depression, anxiety disorders and COVID-19 severity and mortality? A multicenter retrospective cohort study conducted in 50 hospitals in Germany

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### ABSTRACT

**Background:** The aim of this retrospective cohort study was to investigate associations between depression and anxiety disorder and the risk of COVID-19 severity and mortality in patients treated in large hospitals in Germany.

**Methods:** This retrospective study was based on anonymized electronic medical data from 50 public healthcare service hospitals across Germany. Multivariable logistic regression models were used to study associations between depression, anxiety and mechanical ventilation and mortality due to COVID adjusted for age, sex, time of COVID-19 diagnosis, and pre-defined co-diagnoses.

**Results:** Of 28,311 patients diagnosed with COVID-19, 1970 (6.9%) had a diagnosis of depression and 369 (1.3%) had a diagnosis of anxiety disorder prior to contracting COVID-19. While multivariable logistic regression models did not indicate any association between depression diagnosis and the risk of mechanical ventilation, depression was associated with a decreased risk of mortality (OR: 0.71; 95% CI: 0.53–0.94). There was no association between anxiety disorders and risk of mortality, but there was a strong positive association between anxiety disorders and the risk of mechanical ventilation (OR: 2.04; 95% CI: 1.35–3.10).

**Conclusion:** In the present study, depression and anxiety disorder diagnoses were not associated with increased COVID-19 mortality. Anxiety disorder was strongly associated with an increased risk of mechanical ventilation. Further studies are needed to clarify how depression and anxiety disorders may influence COVID-19 severity and mortality.

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## 1. Introduction

As of September 7, 2022, more than 600 million people globally have contracted COVID-19, while the number of related deaths has exceeded six million (World Health Organization 2022). In Germany, the respective figures are 32 million positive cases and 148,000 deaths (World Health Organization 2021).

Previous research has shown that people with psychiatric disorders not only have an increased risk of mortality in general (Plana-Ripoll et al., 2019) but also an increased risk of COVID-19 mortality (Vai et al., 2021; Nemani et al., 2021). However, there were relevant discrepancies between these studies with regard to the types of mental disorder examined.

A meta-analysis of 21 studies including >90 million individuals found significantly higher odds of COVID-19 mortality (OR, 1.51) in persons with preexisting mood disorders (Ceban et al., 2021). Another meta-analysis based on 23 studies comprising 1.5 million patients with COVID-19 and mood disorders found a significant association between mood disorders and COVID-19 mortality (OR: 1.99) but not anxiety disorders (OR: 1.07) (Vai et al., 2021). However, neither of these meta-analyses distinguished between depression, mania, and bipolar disorders.

In a study conducted in California, US, Azar et al. reported significantly higher odds of COVID-19 mortality among those with comorbid depression compared to those without (OR, 2.64) for COVID-19-positive patients with comorbid depression (Azar et al., 2020). In a retrospective case-control study by Douville et al., also conducted in the US, no significant associations were identified between depression and COVID-19-related mechanical ventilation or mortality among hospitalized patients, although the odds of mortality were increased in patients with depression (1.71; 95% CI: 0.87–3.37). However, this association was not significant, likely owing to small patient numbers ( $n = 398$ ).

In another study by Poblador-Plou et al. including 4412 individuals from Spain, there was no association between anxiety disorders and COVID-19 mortality (Poblador-Plou et al., 2020).

Teixeira et al. analyzed nationwide electronic health record data from more than 2.5 million patients in the US. In this study, COVID-19 patients with comorbid anxiety disorders were found to have a 2.4 times greater risk of mortality than those without anxiety disorders (Teixeira et al., 2020). In a recent study, Catalan et al. analyzed data on 157,246 people from the Basque Country (Spain) and observed that anxiety disorders [OR: 1.54] were associated with an increased risk of hospital admission, but were not associated with a higher mortality risk among admitted patients (Catalan et al., 2022).

Although several original studies and meta-analyses have advanced the field, there are significant differences between findings on the impact of depression and anxiety disorders on COVID-19 severity and mortality. The majority of the aforementioned studies were conducted during the first year of the COVID-19 pandemic and it is possible that the effects of psychiatric disorders on COVID-19 severity and mortality have changed over time. Finally, there is a lack of studies on this topic conducted in Germany.

Therefore, the aim of this retrospective cohort study was to investigate associations between depression, anxiety disorder, and the risk of COVID-19 severity and mortality in patients treated in large hospitals in Germany.

## 2. Methods

### 2.1. Study population

This retrospective study based on anonymized electronic medical data from public hospitals across Germany, all belonging to the same hospital group, included 28,311 patients with a confirmed COVID-19 diagnosis (ICD-10 U07.1) hospitalized between March 11, 2020 and July 20, 2022.

Initially, data were collected as part of the “CORONA Germany” study (Clinical Outcome and Risk in hospitalized COVID-19 patients), a multicenter observational, prospective, epidemiological cohort study. All data collected from the data repository were validated using the hospital network’s quality management database. The initial results of the prospective study have been published previously (Gessler et al., 2021; Gunawardene et al., 2021). The study was approved by the ethics committee of the General Medical Council (Aerztekammer) for the City of Hamburg and the ethics committee of the General Medical Council (Aerztekammer) for the City of Munich.

Demographic data (age, sex), COVID-19 relevant data (ventilation, mortality), time of COVID-19 diagnosis, and co-diagnosis data were used for the present study.

### 2.2. Study outcome

The main outcome of the study is associations between unipolar depression (ICD-10: F32, F33) and anxiety disorders (ICD-10: F41) diagnosed prior to COVID-19 and the risk of mechanical ventilation and mortality among COVID-19 patients.

### 2.3. Statistical analyses

Based on the dominance of the respective variants, the COVID-19 variant was defined as non-omicron (all cases from March 2020 to December 2021) or omicron (all cases from January 2022 to July 2022).

First, baseline characteristics of study patients were calculated as proportions (sex, co-morbidities, probable COVID-19 variant) or mean (SD) (age) separately for patients with and without depression and anxiety disorders. Co-diagnoses included cancer (ICD-10: C00–C97), diabetes mellitus (ICD-10: E10–E14), lipid metabolism disorder (ICD-10: E78), obesity (ICD-10: E66), heart failure (ICD-10: I50), ischemic heart disease (ICD-10: I20–I25), cerebrovascular disease (ICD-10: I60–I69), and cirrhosis of the liver (ICD-10: K70.3, K74) as these diagnoses are known to be common causes of mortality.

Multivariable logistic regression models were used to study associations between depression and anxiety and mechanical ventilation and mortality adjusted for age, sex, time of COVID-19 diagnosis, and co-diagnoses. P-values <0.05 were considered statistically significant. All analyses were carried out using R version 4.2.0 (2022-04-22). The results of the logistic regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

## 3. Results

A total of 28,311 patients diagnosed with COVID-19 were available for analyses. There was a strong relationship between death and the application of ventilation. In total, 3074 patients (10.9%) received ventilation, of whom 40.0% died; of the 25,237 patients without ventilation, 10.0% died.

Of the 28,311 study patients, 1970 (6.9%) had a diagnosis of depression and 369 (1.3%) had a diagnosis of an anxiety disorder. Table 1 shows the baseline characteristics of study patients. Both patients with depression and patients with anxiety disorders were significantly younger (depression: 63 years vs. no depression: 66 years; anxiety disorders: 59 years vs. no anxiety disorders 65 years) and more likely to be female (62.6% vs. 47.5% for depression vs. no depression and 61.2% vs. 48.4% for anxiety disorder vs. no anxiety disorders) than patients without these psychiatric disorders. Patients with anxiety disorders had a higher prevalence of obesity (9.2% vs. 5.3%) than patients without anxiety.

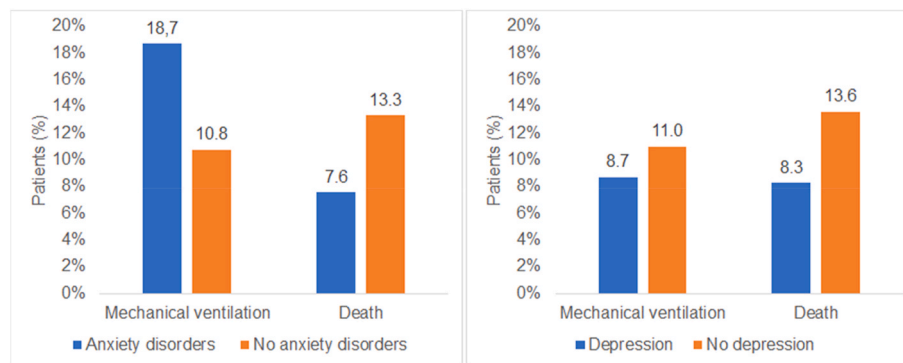
Fig. 1 shows the prevalence of mechanical ventilation and mortality in patients with and without depression and anxiety disorders. Some 8.7% of depression patients and 11.0% of non-depression patients received mechanical ventilation, and 8.3% of depression patients and 13.6% of non-depression patients died. 18.7% of anxiety disorder

**Table 1**  
Baseline characteristics of study patients with and without depression and anxiety disorder diagnosis.

Variable	Patients without depression (N = 26,341) <sup>a</sup>	Patients with depression (N = 1970) <sup>a</sup>	P-value <sup>b</sup>	Patients without anxiety disorder (N = 27,942) <sup>a</sup>	Patients with anxiety disorder (N = 369) <sup>a</sup>	P-value <sup>b</sup>
Female	47.5	62.6	<0.001	48.4	61.2	<0.001
Age (Mean, SD)	66 (21)	63 (22)	<0.001	65 (21)	59 (19)	<0.001
Cancer	5.5	4.0	0.004	5.4	7.0	0.15
Diabetes mellitus	22.7	20.0	0.005	22.6	19.0	0.10
Lipid metabolism disorder	15.1	17.8	0.001	15.3	13.0	0.22
Obesity	5.2	6.3	0.036	5.3	9.2	<0.001
Heart failure	14.3	15.3	0.22	14.4	11.1	0.07
Ischemic heart disease,	13.9	12.7	0.14	13.8	12.5	0.46
Cerebrovascular disease	7.4	10.4	<0.001	7.6	6.2	0.32
Cirrhosis of the liver	0.9	0.9	0.85	0.9	0.3	0.27
Omicron variant	41.0	44.1	0.006	41.2	40.4	0.75
No omicron variant	59.0	55.9		58.8	59.6	

<sup>a</sup> Data are presented as percentages unless otherwise specified.

<sup>b</sup> Welch Two Sample *t*-test; two-sample test for equality of proportions.



**Fig. 1.** Proportion of patients with COVID-19-related ventilation and mortality depending on depression and anxiety diagnosis.

patients and 10.8% of non-anxiety disorder patients received mechanical ventilation, and 7.6% of anxiety disorder patients and 13.3% of non-anxiety disorder patients died (Fig. 1).

Although the multivariable logistic regression found no association between depression diagnosis and the risk of mechanical ventilation, depression was associated with a decrease in the risk of mortality (OR: 0.71; 95% CI: 0.53–0.94). There was no association between anxiety disorders and the risk of death, but there was a strong positive association between anxiety disorders and the risk of mechanical ventilation (OR: 2.04; 95% CI: 1.35–3.10) (Table 2).

**Table 2**  
Association between depression, anxiety disorders, ventilation and death due to COVID-19 in hospitalized patients.

Variable	Odds Ratio (95% CI) <sup>a</sup>	P-value
Depression		
Mechanical ventilation	1.13 (0.89–1.43)	0.306
Death	0.71 (0.53–0.94)	0.020
Anxiety disorders		
Mechanical ventilation	2.04 (1.35–3.10)	<0.001
Death	1.01 (0.58–1.78)	0.964

<sup>a</sup> Multivariable logistic regression model adjusted for age, sex, cancer, diabetes mellitus, lipid metabolism disorder, obesity, heart failure, ischemic heart disease, cerebrovascular disease, cirrhosis of the liver, and COVID-19 variant.

## 4. Discussion

### 4.1. Main findings

This retrospective study including more than 28,000 COVID-19 patients treated in 50 Asklepios hospitals in Germany between March 2020 and July 2022 showed that neither depression nor anxiety disorder were associated with increased COVID-19 mortality; indeed, we actually observed a negative association for depression. Furthermore, anxiety disorders were strongly associated with a risk of mechanical ventilation.

### 4.2. Interpretation of findings

Recently, a substantial body of research has focused on the impact of depression and anxiety on COVID-19-related mortality. In some studies, depression was associated with an increased mortality risk (Atkins et al., 2020; Azar et al., 2020; Wang et al., 2021). Our study does not confirm a positive association between depression and COVID-19 mortality.

One finding of this study which is difficult to interpret is the negative association we found between depression and COVID-19 mortality. This cannot be explained by the younger age or by the higher proportion of women in the depression group, since the regression analysis corrected for these factors and the negative association was not observed for the demographically similar anxiety group. COVID-19 severity is actually thought to be responsible for the increased mortality risk, and it is possible that depression patients in this study had milder COVID-19 symptoms. Wang et al. showed that chronic depression and loneliness were each associated with subsequent COVID-19 hospitalization at the same severity level (Wang et al., 2022). The study of Oskotsky et al.,



2021 supported evidence that selective serotonin reuptake inhibitors (SSRIs) may be associated with reduced severity of COVID-19 as well as COVID-19 mortality. As many depression patients usually receive SSRI, this may be one of the possible reasons for reduced mortality in our study.

However, this finding should be verified in further studies.

The discrepancy between the findings of the published literature and the present study can be explained by the fact that COVID-19 mortality has decreased since the beginning of the pandemic (Fan et al., 2021; Jones et al., 2021).

Regarding anxiety disorders and COVID-19 death, our findings are in line with published sources (Poblador-Plou et al., 2020; Catalan et al., 2022). However, the strong association between anxiety disorders and mechanical ventilation in our study is a novel finding. Several studies have described respiratory manifestations of anxiety disorders in the past. Sardinha et al. discussed causes, consequences, and therapeutic implications of hyperventilation syndromes among panic disorder patients (Sardinha et al., 2009). Nardi et al. explained that panic disorder is associated with respiratory abnormalities such as enhanced CO<sub>2</sub> sensitivity (Nardi et al., 2009). The symptom of breathlessness can occur in the case of respiratory disease but also in patients with anxiety disorders. There is a two-way relationship as panic can cause respiratory difficulties and respiratory difficulties can cause panic (Williams and Carel, 2018). COVID-19 patients with comorbid anxiety disorder who experience breathing difficulties may likely find these breathing symptoms particularly frightening and severe. Finally, these symptoms can cause panic attacks, which in turn cause further breathing difficulties. In such cases, anxiety disorder patients may more often need mechanical ventilation, although their objective COVID-19 severity is not associated with an increased risk of death.

In the total population of this study, deaths were higher among patients who received mechanical ventilation than among patients without ventilation. This supports the assumption that mechanical ventilation is applied in patients with greater COVID-19 severity. This trend has already been observed in another large German study (Hobohm et al., 2022), where 5.3 of survivors and 14.2% of non-survivors received mechanical ventilation. Our study shows that the positive relationship between ventilation and mortality observed for the overall COVID-19 population is not necessarily present in patients with anxiety disorders.

#### 4.3. Strengths and limitations

Two major strengths of this study are the large sample size ( $n = 28,311$ ) and the inclusion of patients diagnosed with COVID-19 over a long period of the pandemic from March 2020 to July 2022. However, our study is also subject to a number of limitations. First, both depression and anxiety disorder diagnosis seem to be underdiagnosed in our cohort as their prevalence in this study is much lower than the prevalence reported for the total population in Germany (Steffen et al., 2020; Niermann et al., 2021; Erhardt et al., 2022). Second, no information was available on psychiatric disease severity. Third, although different chronic conditions were used for adjustment in regression models, other diseases which were not included could have an impact on the study outcome. Furthermore, no detailed information is available on the causes of death in those patients who died. Most but not all mortality cases listed COVID-19 as the main cause of death. In addition, no medications used for COVID-19 therapy and no other medications were analyzed. Information on the vaccination status of the patients included in the study is also missing. Furthermore, given that this study only included patients treated in hospitals, the associations found in this study cannot be generalized to patients treated outside of hospitals. Finally, viral variants were not determined individually for patients. Variants were assigned in accordance with the predominant variant at the time the patient was diagnosed with COVID-19 and a distinction was only made based on whether patients were diagnosed before or since the omicron variant emerged (1/1/2022).

## 5. Conclusions

This study including approximately 28,000 patients treated in Asklepios hospitals in Germany between 2020 and 2022 found that depression and anxiety disorder diagnoses were not associated with increased COVID-19 mortality. Anxiety disorder was strongly associated with an increased risk of mechanical ventilation. Further studies are needed to investigate how depression and anxiety disorders may influence COVID-19 severity and mortality.

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## Author contributions

KK contributed to the design of the study, managed the literature searches, wrote the first draft of the manuscript, and corrected the manuscript. PW and JF contributed to the study design and performed the statistical analyses. NG and MW revised the manuscript. DA, LJ, MG, TH, AK, RS, LS, and SS corrected the manuscript. All authors contributed to and have approved the final manuscript.

## Declarations of competing interest

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MAW has consulted with Allergan/Abbvie and received remuneration for talks from Allergan/Abbvie, Biogen, and Schwabe, but not in connection with the submitted work.

All other authors declare that they have no competing financial interests.

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