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Baseline Anxiety and Depression and Risk for ICU Delirium: A Prospective Cohort Study

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OBJECTIVES: Anxiety and depression are common mental disorders in adults admitted to the ICU. Although depression increases postsurgical delirium and anxiety does not, their associations with ICU delirium in critically ill adults remain unclear. We evaluated the association between ICU baseline anxiety and depression and ICU delirium occurrence.

DESIGN: Subgroup analysis of a prospective cohort study.

SETTING: Single, 36-bed mixed ICU.

PATIENTS: Nine-hundred ninety-one ICU patients admitted with or without delirium between July 2016 and February 2020; patients admitted after elective surgery or not assessed for anxiety/depression were excluded.

INTERVENTION: None.

MEASUREMENTS AND MAIN RESULTS: The Hospital Anxiety and Depression Scale questionnaire was administered at ICU admission to determine baseline anxiety and depression. All patients were assessed with the Confusion Assessment Method for the ICU (CAM-ICU) q8h; greater than or equal to 1 +CAM-ICU assessment and/or scheduled antipsychotic use represented a delirium day. Multivariable logistic and Quasi-Poisson regression models, adjusted for ICU days and nine delirium risk variables ("Pre-ICU": age, Charlson Comorbidity Index, cognitive impairment; "ICU baseline": Acute Physiology and Chronic Health Evaluation-IV, admission type; "Daily ICU": opioid and/or benzodiazepine use, Sequential Organ Failure Assessment score, coma), were used to evaluate associations between baseline anxiety and/or depression and ICU delirium. Among the 991 patients, 145 (14.6%) had both anxiety and depression, 78 (7.9%) had anxiety only, 91 (9.2%) had depression only, and 677 (68.3%) had neither. Delirium occurred in 406 of 991 total cohort (41.0%) patients; in the baseline anxiety and depression group, it occurred in 78 of 145 (53.8%), in the anxiety only group, 37 of 78 (47.4%), in the depression only group, 39 of 91 (42.9%), and in the group with neither in 252 of 677 (37.2%). Presence of both baseline anxiety and depression was associated with greater delirium occurrence (adjusted odds ratio, 1.99; 95% CI, 1.10–3.53; $p = 0.02$) and duration (adjusted risk ratio, 1.62; 95% CI, 1.17–2.23; $p < 0.01$).

CONCLUSIONS: Baseline anxiety and depression are associated with increased ICU delirium occurrence and should be considered when delirium risk reduction strategies are being formulated.

KEY WORDS: anxiety; depression; delirium; intensive care; mental disorders

Anxiety and depression, two of the most common mental disorders in the general population, are present in up to 22% and 12% of adults, respectively, who are admitted to the ICU (1). Characterization of the predisposing and precipitating risk factors for delirium is important when developing delirium reduction efforts (2, 3). Emerging evidence suggests depression shares many mechanistic pathways with delirium (4). Presurgical

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depression is strongly associated with postsurgical delirium after cardiac surgery (5), but presurgical anxiety is not (6). However, risk factors for delirium between cardiac surgical patients (who are usually not critically ill and often transition through the ICU quickly) and those of other ICU populations are different (2, 7).

Studies evaluating the association between mental disorders before ICU admission and ICU delirium occurrence have reported conflicting results and have important limitations (8–11). Study populations have been small, the presence of anxiety and/or depression has not been rigorously evaluated, trained evaluators have not conducted delirium assessments, and the presence of established baseline and ICU daily factors for delirium has not been rigorously considered. Given these limitations, we sought to evaluate the association between baseline anxiety and/or depression and delirium occurrence and duration in a large cohort of critically ill adults.

METHODS

This is a subgroup analysis of the Monitoring cOnsequeNces of InTensive care fOR Intensive Care patients (MONITOR-IC) prospective cohort study (ClinicalTrials.gov: NCT03246334) conducted in a 36-bed mixed ICU at Radboud University Medical Center (Radboud UMC) (12). The study included consecutive Dutch-speaking adult patients (≥16 yr old) with an expected life expectancy greater than or equal to 48 hours who were admitted to the ICU for greater than or equal to 12 hours, regardless of delirium presence, between July 2016 and February 2020. Patients admitted to the ICU after elective surgery were excluded due to their generally lower severity of illness and reduced risk for delirium (7). Patients not evaluated with the Hospital Anxiety and Depression Scale (HADS) at the time of ICU admission were also excluded. This study was approved by the ethics committee of the Radboud UMC (no 2016-2724) on 4 May 2016. Each participant, or their legal representative, provided written informed consent. All research procedures were conducted in accordance with the ethical standards of the Radboud UMC ethics committee and Helsinki Declaration of 1975.

The baseline prevalence of anxiety and depression was measured using HADS-Anxiety (A) and HADS-Depression (D) at the time of ICU admission. If a patient was too ill to participate in one, or both, of the HADS assessments, then a proxy (e.g., family) completed the questionnaire. A score greater than or equal to 8 of 21 on either subscale was deemed to represent clinically significant symptoms of anxiety or depression (12). Current use of antidepressants and benzodiazepines, common psychiatric medications used to treat anxiety and/or depression, were verified by pharmacists at the time of ICU admission. Well-trained ICU nurses assessed all patients without coma (Richmond Agitation Sedation Scale= –4/–5) for delirium using the Confusion Assessment Method for the ICU (CAM-ICU) every 8 hours (13, 14). A delirium day was defined by greater than or equal to 1 +CAM-ICU assessment and/or scheduled antipsychotic use. This definition for delirium has been used in other trials given concerns about the reduced sensitivity of the CAM-ICU when it is used by bedside clinicians (vs researchers) even when clinicians are well-trained (15, 16).

Data on ICU days and potential delirium risk variables ("Pre-ICU": age, modified Charlson Comorbidity Index [17], presence of cognitive impairment [the abbreviated 14-item Cognitive Failure Questionnaire (CFQ-14) ≥ 43/100] [18]; "ICU baseline:" Acute Physiology and Chronic Health Evaluation-IV [19], admission type [medical, urgent surgery]; "Daily ICU": opioid [≥ 10 mg IV morphine equivalents/d] [20] or benzodiazepine [≥ 5 mg IV midazolam equivalents/day] [21] use, average Sequential Organ Failure Assessment score [22], occurrence of coma) were collected. Random data missingness was low (< 5%) for all variables. Data on HADS and CFQ-14 were collected and entered into the MONITOR-IC study database (overseen by M.Z. and M.v.d.B.); data were checked regularly to identify out-of-range and inconsistent responses (12). The MONITOR-IC database was merged with patient-level Radboud UMC electronic health record data by an author (R.K.) and verified by an author (M.v.d.B.).

We used multivariable logistic regression and Quasi-Poisson regression to estimate the association between baseline anxiety and/or depression and ICU delirium occurrence and days. Both regression models were adjusted for ICU days and the nine delirium risk variables. We subsequently performed sensitivity analyses by including pre-ICU antidepressant/benzodiazepine use as independent variable into both models. To investigate the influence of the HADS assessment participant (i.e., patient vs proxy) on the association between anxiety and depression and delirium occurrence

and duration additional sensitivity analyses were performed. To investigate the possible interference of delirium on the HADS assessments, an exploratory analysis that excluded patients with delirium at the time of ICU admission was conducted. A *p* value of less than 0.05 was considered statistically significant. All analyses were performed using R Version 4.0.3. (R Foundation for Statistical Computing).

RESULTS

Of the 2,853 patients included in the parent MONITOR-IC study, 346 were excluded from this subgroup analysis because they were admitted to the ICU less than or equal to 12 hours, 1,482 because they were admitted to the ICU for planned elective surgery, and 34 because the HADS questionnaire was not completed. Among the 991 patients included in our analysis, the HADS questionnaire was primarily completed by the patient (634 [64.0%]). A proxy alone completed one-third of the assessments (337 [34.0%]). For 20 patients (2.0%), the person completing the HADS questionnaire (i.e., patient or proxy) was not documented. At baseline, 145 patients (14.6%) had both anxiety and depression, 78 (7.9%) had anxiety alone, 91 (9.2%) had depression alone, and 677 (68.3%) had neither. Anxiety, depression, or both were less frequently reported when the patient answered the HADS questionnaire (177/634 [27.9%]) than the proxy (127/337 [37.7%]; $p < 0.01$). Patients with both anxiety and depression (vs patients with neither) were more likely to have baseline cognitive impairment (**Table 1**). Study covariates between patients with baseline anxiety only and depression only (vs those with neither) are presented in **Supplemental Table 1** (Supplemental Digital Content 1, http://links.lww.com/CCX/B44).

Delirium occurred in 406 of the 991 patients (41.0%) for a median (interquartile range) 2 days (1–5 d); 76 of the 406 patients (18.7%) had delirium at the time of ICU admission. Among patients with both anxiety and depression, delirium occurred in 78 of 145 patients (53.8%) for 3 days (1–5 d); in patients with anxiety

TABLE 1.
Comparison of Covariates Between Patients With and Without Anxiety and Depression

Variables	Both Anxiety and Depression, *N* = 145	Neither Anxiety Nor Depression, *N* = 677	*p*
Pre-ICU admission			
Psychiatric medication(s) use, *n* (%)	7 (5)	15 (2)	0.09
Age, median (IQR)	61 (53–70)	62 (49–71)	0.59
Modified Charlson Comorbidity Index, median (IQR)	2 (1–4)	2 (1–4)	0.17
Cognitive impairment, *n* (%)[a]	18 (12)	14 (2)	< 0.01
ICU baseline			
Admission type, *n* (%)			0.06
Medical	103(71)	423 (62)	
Urgent surgery	42 (29)	254 (38)	
Acute Physiologic and Chronic Health Evaluation IV score, median (IQR)	67(54-82)	68(52-84)	0.62
ICU clinical			
Sequential Organ Failure Assessment Score, median (IQR)	6 (4-9)	6 (4-8)	0.20
Presence of coma, *n* (%)	53 (37)	248 (37)	1.00
Opioid exposure, *n* (%)	49 (34)	189 (28)	0.19
Benzodiazepine exposure, *n* (%)	33 (23)	122 (18)	0.23
ICU days, median (IQR)	1.6(0.6-4.1)	1.6(0.8-3.1)	0.55

IQR = interquartile range.
[a]Cognitive Failure Questionnaire Score ≥ 43.

alone, delirium occurred in 37 of 78 patients (47.4%) for 2 days (1–5 d); in patients with depression alone, delirium occurred in 39 of 91 patients (42.9%) for 2 days (1–5 d); and in patients with neither anxiety nor depression, delirium occurred in 252 of 677 (37.2%) for 2 days (1–5 d). All collected variables were significantly different between the delirium and nondelirium groups except for baseline cognitive impairment and admission type (**Supplemental Table 2**, Supplemental Digital Content 1, http://links.lww.com/CCX/B44).

Presence of both anxiety and depression at ICU baseline was associated with greater delirium occurrence (adjusted odds ratio [aOR], 1.99; 95% CI, 1.10–3.53; $p = 0.02$) and duration (adjusted risk ratio [aRR], 1.62; 95% CI, 1.17–2.23; $p < 0.01$) (**Table 2**). Pre-ICU treatment with a medication to treat anxiety/depression did not affect these results. Presence of anxiety or depression alone was not associated with delirium occurrence or duration (Table 2). The person participating in the HADS assessments (i.e., patient vs proxy) had only a minor effect on the association between anxiety and depression and delirium occurrence and duration (**Supplemental Table 3**, Supplemental Digital Content 1, http://links.lww.com/CCX/B44). When the 76 patients with delirium at the time of ICU admission were excluded from the analysis, the presence of both anxiety and depression was associated with a lower, and no longer significant, association with delirium occurrence and a lower, but still significant, duration of delirium (**Supplemental Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCX/B44).

DISCUSSION

Rigorously establishing risk factors for delirium in critically ill adults is important given their value in informing delirium reduction efforts (2, 3). Our study is the first to rigorously evaluate the risk of baseline anxiety and depression, each common mental health issues, and ICU delirium occurrence. After controlling for nine established baseline and daily ICU delirium risk factors, we report that the presence of anxiety and

TABLE 2.
Association Between Anxiety/Depression and Delirium Occurrence and Days With Delirium

	ICU Delirium Occurrence			
	Model 1		Model 2	
Variables	aOR (95% CI)	*p*	aOR (95% CI)	*p*
Both anxiety and depression	1.99 (1.10–3.53)	0.02	1.92 (1.06–3.41)	0.03
Anxiety only	1.24 (0.53–2.70)	0.60	1.16 (0.49–2.56)	0.72
Depression only	1.83 (0.94–3.47)	0.07	1.81 (0.92–3.45)	0.08
Pre-ICU psychiatric medication use			2.89 (0.94–8.45)	0.06
	ICU Days With Delirium			
	Model 3		Model 4	
	aRR (95% CI)	*p*	aRR (95% CI)	*p*
Both anxiety and depression	1.62 (1.17–2.23)	< 0.01	1.62 (1.16–2.23)	< 0.01
Anxiety only	1.01 (0.61–1.60)	0.96	1.00 (0.60–1.59)	0.99
Depression only	1.18 (0.70–1.86)	0.51	1.18 (0.70–1.87)	0.51
Pre-ICU psychiatric medication use			1.12(0.53–2.09)	0.74

aOR = adjusted odds ratio, aRR = adjusted risk ratio, CI = confidence ratio.

Models 1 and 3 adjusted for age, Charlson Comorbidity Index, cognitive impairment, Acute Physiologic and Chronic Health Evaluation IV score, admission type, opioid use, benzodiazepine use, Sequential Organ Failure Assessment score, presence of ICU coma, and days in ICU. Models 2 and 4 adjusted for baseline psychiatric medication use (antidepressants, benzodiazepines) and all covariates used in Models 1 and 3.

depression at the time of ICU admission is associated with a two-fold risk of delirium occurrence during the ICU admission, and if delirium occurs, it is associated with a longer duration (1.5 times as long).

These results highlight the importance of determining whether patients admitted to the ICU have symptoms of anxiety, depression, or both, with widely available, validated, screenings tools like the Generalized Anxiety Disorder-7 (for anxiety) and the Patient Health Questionnaire-9 (for depression) or asking primary care physicians about pre-existing mental disorders. The presence of anxiety and/or depression before or at the time of ICU admission should be documented in the patient's record, and used, along with other known risk factors for ICU delirium to formulate delirium reduction plans. In general, home medications used for anxiety and/or depression such as benzodiazepines and/or selective serotonin reuptake inhibitors should be continued in the ICU given the potential concern for withdrawal if they are suddenly discontinued.

Our results also highlight future research questions. Although the presence of baseline depression alone was weakly associated with delirium, the number of patients with depression alone was far smaller than the number of patients who had both anxiety and depression. Future research needs to disentangle the effect of anxiety, known to be magnified in the ICU setting, on depression-delirium relationships (23).

Although involvement of a patient proxy rather than the patient for the HADS assessment has never been formally validated in either ICU or non-ICU settings, proxies are frequently used in psychologic surveys evaluating anxiety and/or depression (24). Proxies have been shown to be able to reliably evaluate patient pre-ICU quality of life (25). Excluding nonpatient HADS responses might cause sampling bias. The results from our study where proxy respondents were more likely to report anxiety and depression are similar to non-ICU investigations where proxy respondents (vs patients) are more likely to report mental disorders as being more severe (26). The influence of delirium on the validity/reliability of the HADS assessment remains unclear and should be further investigated. The relationship between ICU delirium and post-ICU mortality may be different between incident delirium (first occurring in the ICU) and prevalent delirium (occurring before or after ICU admission) (27). The lack of association we report between baseline anxiety and depression and ICU delirium occurrence in the incident delirium subgroup, while potentially due to a sample size issue, also requires further investigation given the duration of delirium before ICU admission and its phenotype may influence the relationship between anxiety, depression and delirium that persists after the ICU admission (28).

Despite the strengths of our analysis, significant limitations exist. A selection bias may exist in our study given a HADS assessment was not able to be conducted in some patients, although this was rare. Our results may be different in ICUs where the prevalence of delirium is different. There may be residual confounders affecting delirium occurrence we did not consider. Our results may not be generalizable to other countries, like the United States, where use of medications to treat anxiety and depression is more common. For patients chronically taking psychiatric medications, ICU baseline HADS scores may be lower, and a relationship with delirium may have been missed. Although antipsychotics at Radboud UMC are clinically restricted for the treatment of agitated delirium (16), there may have been patients who were treated with an antipsychotic who did not have delirium.

In conclusion, our study results suggest the presence of both anxiety and depression at the time of ICU admission may be associated with twice the risk of delirium in critically ill adults. Further prospective studies, which include more patients taking antidepressant/antianxiety medications and with delirium at the time of ICU admission, are warranted to further evaluate this association.

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