ORIGINAL RESEARCH

Association of Stress Biomarkers With 30-Day Unplanned Readmission and Death

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BACKGROUND: The theory that posthospitalization stress might increase the risk of postdischarge complications has never been investigated.

OBJECTIVE: To assess whether serum levels of stress biomarkers at discharge are associated with readmission and death after an acute-care hospitalization.

DESIGN: We prospectively included 346 patients aged ≥50 years admitted to the department of general internal medicine at a large community hospital between April 8, 2013 and September 23, 2013. We measured the serum levels of several biomarkers at discharge: midregional pro-adrenomedullin, copeptin, cortisol, and prolactin. All patients were followed for up to 90 days after discharge (none was lost to follow-up). The main outcome was first unplanned readmission or death within 30 days after hospital discharge. We assessed the additional value of biomarkers to 2 validated readmission prediction scores: the LACE index (Length of stay, Admission Acuity, Charlson Comorbidity Index, and number of Emergency department visits within preceding 6 months) and the HOSPITAL score (Hemoglobin level at discharge, discharge from Oncology service, Sodium level at discharge, any Procedure performed during index hospitalization, Index admission Type, number of Admissions within preceding 12 months, and Length of stay).

RESULTS: Forty patients (11.6%) had a 30-day unplanned readmission or death. High serum copeptin and cortisol levels were associated with an increase in the odds of unplanned readmission or death (odds ratios [95% confidence interval] 2.69 [1.29-5.64] and 3.43 [1.36, 8.65], respectively). We found no significant association with midregional pro-adrenomedullin or prolactin. Furthermore, these stress biomarkers increased the performance of two readmission prediction scores (LACE index and HOSPITAL score).

CONCLUSION: High serum levels of copeptin and cortisol at discharge were independently associated with 30-day unplanned readmission or death, supporting a possible negative effect of hospitalization stress during the postdischarge period. Stress biomarkers improved the performance of prediction models and therefore could help better identify high-risk patients. *Journal of Hospital Medicine* 2017;12:523-529. © 2017 Society of Hospital Medicine

It has been theorized that the physiologic stress that hospitalized patients experience accounts for their transient vulnerability after discharge, or *posthospital syndrome*.[1] Their acute illness and life-habit changes during hospitalization result in continued impairment of physiologic systems after discharge, and this impairment might leave them more susceptible to new health threats.[1] However, the theory that the stress experienced after a hospitalization might be associated with readmission has never been investigated.

Four biomarkers of the hypothalamic-pituitary-adrenal (HPA) axis may help quantify posthospitalization stress: (1) midregional pro-adrenomedullin (ADM), a precursor reflecting adrenomedullin activity[2]; (2) copeptin (the C-ter-

minal part of prepro-vasopressin, produced by the hypothalamus in response to stress[3,4]), the level of which closely correlates to the vasopressin level but is more stable and lacks circadian rhythm fluctuations[5-7]; (3) cortisol, released by the adrenal cortex in response to stress; and (4) prolactin, an indicator of HPA axis activity. These 4 stress biomarkers have been related to the severity, complications, or mortality of several diseases.[3,5,8-17] Besides explaining the hypothetical association between posthospitalization stress and readmission and death, these biomarkers might be valuable in predicting which patients are at higher risk for readmission. Indeed, many prediction models have been developed to identify those patients, but most of these models underperform, target only very specific populations, or have not been externally validated.[18]

We hypothesized that the hospitalization stress measured by biomarkers is associated with readmission or death after discharge. In a prospective cohort study, we evaluated the association between 4 stress biomarkers (ADM, copeptin, cortisol, prolactin) and 30-day unplanned readmissions and deaths after an acute-care medical hospitalization, and assessed their additive value to validated readmission prediction scores.

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METHODS

Study Design and Population

Our prospective cohort study included all consecutive patients aged ≥50 years and admitted to the department of general internal medicine at Fribourg Cantonal Hospital in Switzerland between April 8, 2013 and September 23, 2013. Exclusion criteria were discharge on day of admission; death before discharge; discharge to another division, another acute-care hospital, a rehabilitation clinic, or a palliative-care clinic; and refusal or inability to give informed consent. In this hypothesis-generating observational study, we collected data on a convenience sample of patients and did not calculate sample size before data collection. The study was approved by the local ethics committee, and all patients gave informed consent.

Outcomes

The primary outcome was the composite of first unplanned readmission (to any division of any acute-care hospital) or death within 30 days after discharge from index admission. We also included deaths that occurred after discharge, hypothesizing that patients who died may have been readmitted had they lived. The secondary outcome was the same as the primary, but the period was 90 days. Planned readmission was defined as scheduled hospitalization for nonemergent treatment (eg, chemotherapy) or investigation (eg, elective coronarography). All patients were called 6 months after discharge, and readmissions and deaths recorded. If a patient could not be reached directly, we called his or her next of kin, primary care physician, or nursing home, depending on availability. Furthermore, we checked electronic health records for any readmission or death recorded within the Fribourg hospital network, which includes all 3 acute-care hospitals (Fribourg, Riaz, Tavel) in the same canton (state).

Independent Variables

Stress biomarkers. We measured serum levels of 4 stress biomarkers (ADM, copeptin, cortisol, prolactin) at 8 am on an empty stomach on both day of admission and day of discharge. For a patient whose discharge decision was made after 8 hours for the same day, a blood sample was collected as soon as discharge was planned.

Clinical data. Collected data included demographics, history of hospitalization within 6 months before index admission, hospitalization diagnosis, and Charlson Comorbidity Index (CCI), which includes a list of medical conditions that are assigned a number of 1, 2, 3, or 6 points, according to their severity, and which has been associated with mortality.[19]

Causes of Admission, Unplanned Readmission, and Death

Causes of index admission, unplanned readmission, and death were obtained from medical records. We used our consensus opinion and a previous analysis[20] to classify these causes by body system, and added 2 categories, cancer and infection (both associated with readmission[20]). The resulting 9 categories were (1) cancer, (2) respiratory disorder, (3) infectious disorder, (4) neurologic disorder (including dementia, psychiatric disorder, alcohol disorder, and intoxication), (5) gastrointestinal disorder, (6) osteoarticular disorder, (7) renal disorder, (8) cardiovascular disorder (including ischemic disease and heart failure), and (9) other.

Additional Performance With Existing Predictive Models

To better define the explanatory power of biomarkers to predict our outcome, we assessed the performance improvement of 2 validated readmission prediction scores by adding the stress biomarkers. As large effect sizes from additional predictors are needed to increase the power discrimination of a model, a significant performance improvement would further support the biomarkers' important explanatory power. The 2 prediction scores tested were the LACE index (Length of stay, Admission Acuity, CCI, number of Emergency department visits within preceding 6 months[21]) and the HOSPITAL score (Hemoglobin level at discharge, discharge from Oncology service, Sodium level at discharge, any Procedure performed during index hospitalization, Index admission Type, number of Admissions within preceding 12 months, Length of stay). As we did not have an oncology service, we replaced "discharge from oncology service" with "active diagnosis of cancer." "Length of stay" was tailored to the median in Switzerland (8 days instead of 5 days; Supplement Table 1).[22,23]

Data Analysis

Continuous variables were presented as medians with interquartile ranges (IQRs) because of their non-normal distribution, and categorical variables were presented as frequencies and percentages. We compared medians using the nonparametric K-sample test on the equality of medians, and compared frequencies using the Pearson χ^2 test. The discriminatory power of each biomarker in predicting readmission and death was calculated with the area under the receiver operating characteristic (ROC) curve (AUROC), using serum levels at discharge to better reflect the postdischarge period. Cutoff levels were selected by taking the best compromise between sensitivity and specificity according to the ROC curves (point nearest top left corner).[24]

Univariate logistic regression analysis was used to test the prediction of 30-day and 90-day unplanned readmission or death by each biomarker. We built 2 different multivariate models: one adjusting for age and LACE index points[21] and the other adjusting for age and HOSPITAL score.[22,23]

To explore any association between reduction of stress during hospitalization and postdischarge outcome, we additionally calculated for each biomarker the difference between admission and discharge serum levels and assessed its association with readmission or death by logistic regression analysis. Because of the modification of cortisol serum levels during corticosteroid therapy, we excluded patients who underwent systemic corticosteroid therapy before or during

TABLE 1. Baseline Characteristics of Entire Cohort, and According to Readmission or Death Within 30 Days After Discharge From Index Admission

Variable	Entire Cohort (N = 346)	30-Day Readmission or Death (n = 40)	No 30-Day Readmission or Death (n = 306)
Age, y	73 (64-82)	70 (64-76)	74 (64-82)
Male sex	172 (49.7)	21 (52.5)	151 (49.3)
Charlson Comorbidity Index	7 (5-9)	8 (6-11)	7 (5-9)
Multimorbidity[a]	310 (89.6)	36 (90.0)	274 (89.5)
Previous admission[b]	97 (30.7)	17 (42.5)	80 (26.1)
Hospitalization characteristics			
Elective	13 (3.8)	2 (5.0)	11 (3.6)
Length of stay, d	7 (4-12)	7 (5-13)	7 (4-12)
Infectious disorder	185 (53.5)	31 (77.5)	154 (50.3)
Diagnosis at index admission			
Cancer	27 (7.8)	7 (17.5)	20 (6.5)
Respiratory disorder/COPD[c]	31 (9.0)	4 (10.0)	27 (8.8)
Infectious disorder	70 (20.2)	11 (27.5)	59 (19.2)
Neurologic disorder[c,d]	66 (19.1)	3 (7.5)	63 (20.6)
Gastrointestinal disorder[c]	19 (5.5)	2 (5.0)	17 (5.6)
Osteoarticular disorder[c]	10 (2.9)	4 (10.0)	6 (2.0)
Renal disorder[c]	4 (1.2)	0 (0.0)	4 (1.3)
Cardiovascular disorder[e]	92 (26.6)	5 (12.5)	87 (28.4)
Endocrine disorder	11 (3.2)	2 (5.0)	9 (2.9)
Other	16 (4.6)	2 (5.0)	14 (4.6)

NOTE: Data are n (% of column) or median (interquartile range). Abbreviation: COPD, chronic obstructive pulmonary disease.
[a]Two or more comorbidities as recorded in Charlson Comorbidity Index.
[b]Hospital admission(s) within 6 months preceding index admission.
[c]Other than infection.
[d]Including dementia, psychiatric disorder, alcohol disorder, intoxication.
[e]Including ischemic/thrombotic disorder, congestive heart failure, arrhythmia.

hospitalization for the cortisol analysis (n = 105/346). Patients with a missing biomarker level were excluded from the respective analyses: discharge (ADM, 28 patients; copeptin, 27; cortisol, 24; prolactin, 24) and admission (ADM, 12 patients; copeptin, 15; cortisol, 8; prolactin, 8).

To assess an additional value of the biomarkers to prediction scores, we assessed the accuracy of the HOSPITAL score and LACE index in their original versions[21,22] and after adding each biomarker. We used AUROC to assess the discriminatory power and used the method of DeLong et al.[25] to compare results with and without adding each biomarker. Calibration was evaluated by comparing Hosmer-Lemeshow goodness-of-fit tests ($P > 0.05$ indicates good fit). Risk reclassification was assessed by Net Reclassification Improvement (NRI),[26] quantifying how appropriately a new model reclassifies patients, compared with an old model. Basically, patients without outcome are assigned +1 if correctly reclassified to a lower risk category or –1 if incorrectly reclassified to a higher risk category. $NRI_{nonevent}$ is the sum of all points/ numbers of patients. Conversely, patients with outcome are assigned +1 if correctly reclassified to a higher risk category or –1 if incorrectly reclassified to a lower risk category.

NRI_{event} is the sum of all points/numbers of patients. $NRI_{overall}$ is the sum of NRI_{event} and $NRI_{nonevent}$ ranging from –2 to 2, with a positive value indicating better classification with the new model.

Two-sided $P < 0.05$ was used for statistical significance. All statistical analyses were performed with Stata Release 13.0 (StataCorp).

RESULTS

Among the 530 patients admitted to the ward, 184 were excluded (120 meeting exclusion criteria, 64 unable to give consent, Figure 1). Among the 346 patients included, 11.6% (n = 40) had a 30-day unplanned readmission or death (37 were readmitted, 2 died during readmission, 3 died without readmission). Within 90 days, 26.6% (n = 92) had a readmission or death (84 were readmitted, 10 died during or after readmission, 8 died without readmission).

Clinical Characteristics

Table 1 lists the patients' baseline characteristics. Median age was 73 years (IQR, 64-82 years). Of the 346 patients included, 172 (49.7%) were men. Median CCI was 7 (IQR,
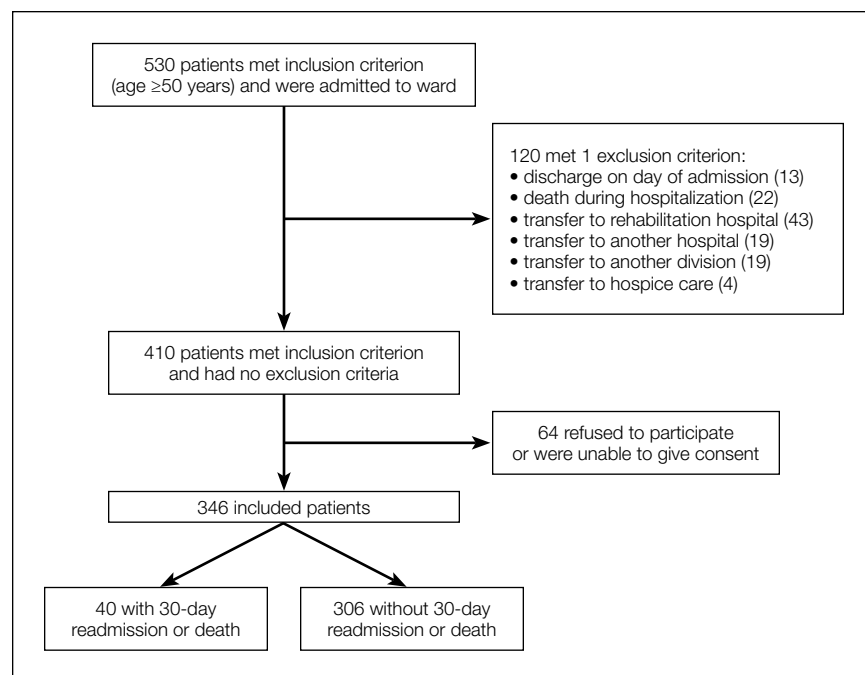
FIG. Study flow diagram.

5-9); according to this index, 310 patients (89.6%) had at least 2 comorbidities. Median length of stay was 7 days (IQR, 4-12 days).

Primary Diagnoses of Admission, Unplanned Readmission, and Death

The 3 main causes of index admission were cardiovascular disorder (n = 92), infectious disorder (n = 70), and neurologic disorder (n = 66). Table 2 lists the causes of readmissions

TABLE 2. Causes of Unplanned Readmissions and Death Within 30 Days of Discharge (n = 40)

Cause	30-Day Readmission (n = 37)[a]	30-Day Death (n = 5)[a]
Cancer	10 (27.0)	3 (60.0)
Infectious disorder	7 (18.9)	—
Respiratory disorder[b]	5 (13.5)	2 (40.0)
Cardiovascular disorder[b,c]	4 (10.8)	—
Osteoarticular disorder[b]	4 (10.8)	—
Neurologic disorder[b,d]	3 (8.1)	—
Gastrointestinal disorder[b]	2 (5.4)	—
Renal disorder[b]	1 (2.7)	—
Other/unknown	1 (2.7)	—

NOTE: Data are n (% of column).
[a]Two patients died after readmission within 30 days.
[b]Other than infection.
[c]Including ischemic/thrombotic disorder, congestive heart failure, arrhythmia.
[d]Including dementia, psychiatric disorder, alcohol disorder, intoxication.

and deaths. A same-diagnosis category between index admission and readmission was found in 17 (45.9%) of the 37 readmitted patients and in 3 (60%) of the 5 patients who died.

Biomarkers and 30-Day Unplanned Readmission or Death

AUROC was 0.53 (95% confidence interval [CI], 0.43-0.63) for ADM, 0.60 (95% CI, 0.50-0.70) for copeptin, 0.59 (95% CI, 0.44-0.73) for cortisol, and 0.56 (95% CI, 0.45-0.66) for prolactin. The difference between admission and discharge levels was not associated with unplanned readmission or death for any of the biomarkers (Supplemental Table 2).

ADM and readmission or death. Median ADM level was not different between patients with and without readmission or death (1.0 nmol/L in each case; *P* = 1.00). The best cutoff level for ADM was 2 nmol/L (sensitivity, 16.7%; specificity, 91.8%). At this level, ADM was associated with a nonstatistically significant 130% increased odds of 30-day readmission or death (*P* = 0.09; Table 3, Supplemental Table 3). Conversely, the association with the 90-day outcome was significant (*P* = 0.02; Table 3, Supplemental Table 4).

Copeptin and readmission or death. Patients with 30-day readmission or death had a higher median copeptin level at discharge than patients without (10.4 pmol/L vs 7.3 pmol/L; *P* = 0.03). At a copeptin level higher than 9 pmol/L (to convert to pg/mL, divide by 0.249; sensitivity, 66.7%; specificity, 59.7%), both 30-day readmission or death (adjusted odds ratio [OR], 2.69; 95% CI, 1.29-5.64; *P* = 0.009) and 90-day readmission or death (adjusted OR, 2.76; 95% CI, 1.56-4.88; *P* < 0.001) were nearly 3 times as likely (Table 3, Supplemental Tables 3 and 4).

Cortisol and readmission or death. Median cortisol was not statistically different between patients with and without the primary outcome (431 nmol/L vs 465 nmol/L; *P* = 0.72). At a cortisol level higher than 590 nmol/L (to convert to µg/dL, divide by 27.59; sensitivity, 54.6%; specificity, 76.4%), 30-day outcome was more than 3 times as likely (adjusted OR, 3.43; 95% CI, 1.36-8.65; *P* = 0.009; Table 3, Supplemental Table 3). At 90 days, only the model that adjusted for age and LACE index points remained statistically significant (*P* = 0.02; Table 3, Supplemental Table 4).

Prolactin and readmission or death. Median prolactin was not statistically different between patients with and without the primary outcome (15.1 µg/L vs 14.1 µg/L; *P* = 0.24). The best cutoff level for prolactin was 23 µg/L (to convert to mIU/L, divide by 0.05; sensitivity, 27.8%; specificity, 82.9%). Prolactin was associated with a nonstatistically significant increased odds of 30-day (*P* = 0.16) and 90-day (*P* = 0.24) readmission or death (Table 3, Supplemental Tables 3 and 4).

TABLE 3. Univariate and Multivariate Logistic Regression for Unplanned Readmission or Death Within 30 Days and 90 Days After Discharge From Index Admission

	OR (95% CI)		
Biomarker Levels	Univariate Analysis	Model Adjusting for Age and LACE Index	Model Adjusting for Age and HOSPITAL Score
30 days after discharge			
ADM, >2 nmol/L[a]	2.36 (0.89-6.29)	2.34 (0.87-6.33)	2.39 (0.88-6.50)
Copeptin, >9 pmol/L[a]	2.62 (1.28-5.39)	2.72 (1.30-5.69)	2.69 (1.29-5.64)
Cortisol, >590 nmol/L[a,b]	3.88 (1.58-9.58)	3.82 (1.54-9.43)	3.43 (1.36-8,65)
Prolactin, >23 µg/L[a]	1.86 (0.84-4.11)	1.86 (0.83-4.13)	1.78 (0.79-3.98)
90 days after discharge			
ADM, >2 nmol/L[a]	2.67 (1.21-5.89)	2.45 (1.08-5.53)	2.76 (1.18-6.47)
Copeptin, >9 pmol/L[a]	2.59 (1.55-4.33)	2.58 (1.50-4.43)	2.76 (1.56-4.88)
Cortisol, >590 nmol/L[a,b]	2.41 (1.21-4.86)	2.35 (1.15-4.78)	1.96 (0.92-4.19)
Prolactin, >23 µg/L[a]	1.63 (0.89-2.99)	1.58 (0.84-2.99)	1.49 (0.76-2.89)

[a]Cutoff levels: best compromise between sensitivity and specificity, identified by receiver operating characteristic curves analysis. Levels are at discharge.

[b]Patients who had systemic corticosteroid therapy before or during hospitalization were excluded (n = 105).

NOTE: Abbreviations: ADM, midregional pro-adrenomedullin; CI, confidence interval; HOSPITAL, Hemoglobin level at discharge, discharge from Oncology service, Sodium level at discharge, any Procedure performed during index hospitalization, Index admission Type, number of Admissions within preceding 12 months, and Length of stay; LACE, Length of stay, Admission Acuity, Charlson Comorbidity Index, and number of Emergency department visits within preceding 6 months; OR, odds ratio.

Additive Value of Biomarkers to HOSPITAL Score and LACE Index

The AUROC for the original HOSPITAL score, 0.70 (95% CI, 0.60-0.80), nonsignificantly increased to 0.76 after adding the biomarkers ($P > 0.14$). For the LACE index, AUROC was 0.59 (95% CI, 0.49-0.68), with a significant 0.10 increase with cortisol ($P = 0.04$) and a near significant increase with copeptin ($P = 0.08$). Calibration remained almost unchanged after adding the biomarkers to both models (Supplemental Table 5). NRI$_{overall}$ was positive for all biomarkers, with statistical significance for copeptin added to the HOSPITAL score (0.47; 95% CI, 0.13-0.79) and for cortisol added to the LACE index (0.62; 95% CI, 0.15-1.06).

DISCUSSION

In this prospective cohort study, 30-day and 90-day unplanned readmission or death was nearly 3 times as likely for patients with high copeptin levels on discharge from an acute-care medical hospitalization, and 30-day readmission or death was more than 3 times as likely for patients with high cortisol levels. High ADM and prolactin levels were not consistently associated with readmission or death. Adding such biomarkers to readmission prediction models improved their performance.

These findings support the theory of posthospital syndrome,[1] which describes a period of vulnerability with increased stress after discharge from an acute-care hospitalization, and which may be associated with adverse outcome. The hormones cortisol and copeptin are strongly related to the stress response in humans.[4,5] As copeptin level has been associated with adverse prognosis for several disorders affecting a wide range of physiologic systems,[3,5,15,27] it may be a valuable biomarker of a stressful condition, even independent of the system affected by the acute illness, and its use

may be widely generalizable, in contrast to predictive factors identified in other studies.[18,28,29]

Although cortisol was independently associated with 30-day readmission or death, and may be an interesting biomarker and less expensive than copeptin, its measurement is limited in patients treated with systemic corticosteroids. Compared with cortisol, copeptin does not undergo diurnal variation, is less affected by corticosteroid therapy, and mirrors stress levels better.[5,7,30,31] Our results showed that, contrary to cortisol, copeptin was also associated with longer term outcome. High ADM level was associated with readmission or death at 90 days only; lack of a significant association at 30 days might be attributable to a lack of power (fewer outcomes at 30 days). Conversely, prolactin level was consistently not associated with outcome. Prolactin may be affected by many drugs that act on the dopaminergic system (eg, domperidone), and therefore its levels may be more difficult to interpret.

Levels of biomarkers were similar to those measured in patients without previously studied conditions (eg, myocardial infarction).[5,8,10,13,14,16,17] In most previous analyses, levels were measured during a stressful event, whereas we measured them at discharge. Therefore, these biomarkers may constitute sensitive markers of remaining stress at discharge.

Our finding that copeptin level was independently associated with readmission or death supports its relevance as a possible simple measure of the risk of adverse postdischarge outcome, independently of disease type and independently of known predictors. Stress biomarkers may therefore be valuable predictors of which patients are at high risk. All these biomarkers can be measured within 30 minutes, extending their use beyond everyday practice, except for the possible need of an extra blood draw.

The most accurate and validated models are the HOSPITAL score (AUROC range, 0.68-0.77[23,32-36]) and the LACE

index (AUROC range, 0.56-0.68[23,34,35,37]). Adding biomarkers to these models improved overall performance (up to 0.10 increase in AUROC), which is remarkable given that, once a particular level of discriminatory power is reached, extremely large effect sizes from additional markers are needed to increase AUROC.[26] Incremental improvement is objectively supported by positive NRI. Our results suggest biomarkers added to prediction models may improve identification of high-risk patients.

We found that less than 50% of the primary diagnoses belonged to the same diagnosis category at readmission and at index admission. This result is in line with previous findings that readmissions were related to the primary diagnosis at index admission in only 22% to 46% of cases,[20,38] and supports our study hypothesis that readmission is related to underlying stress factors often independent of the underlying illness.[1]

Study Limitations and Strengths

Our study had some limitations. First, it was a single-center study with a limited sample size. However, we found significant results within the sample. Second, we could not adjust for drugs that were acting on the dopaminergic system and might have affected prolactin levels. However, such interactions would limit the use of this biomarker in clinical practice anyway. Third, we used specific cutoffs, which might decrease analytical power, in comparison with continuous analyses. However, we followed a recognized method[24] and found a significant association even with categorized levels. Furthermore, the distribution of biomarkers could not be normalized by logarithmic transformation, and cutoff values have the advantage of being integrable into score point systems (eg, HOSPITAL score, LACE index). Fourth, although in 2 models we found consistent associations with several potential confounders, we could not exclude residual confounding. Fifth, this study was not powered to assess the biomarkers' predictive value for readmission and death, which might explain the lack of significant differences between AUROC with and without the biomarkers. For all these reasons, this study should be considered hypothesis-generating.

Our study also had its strengths. First, to our knowledge, this is the first study of the association between stress biomarkers at discharge and unplanned readmission or death. Second, the quality of our data was high, with a low percentage of missing biomarker levels. Third, we excluded planned readmissions. Fourth, we used an unselected medical patient population, which had the noteworthy advantage of widening the generalizability of results.

CONCLUSION

In this prospective cohort study, high copeptin and cortisol levels at discharge were significantly associated with increased odds, ranging from 2-fold to more than 3-fold, of unplanned readmission or death within 30 days after discharge from an internal medicine ward. This finding supports the theory that a physiologic stress that patients experience during hospitalization makes them more susceptible to new

health threats (posthospital syndrome). These biomarkers, copeptin in particular, may help us better identify patients at high risk of early unplanned readmission or death.

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