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Nocturnal respiratory rate as a predictor of mortality in patients with acute coronary syndrome

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ABSTRACT

Background Patients with acute coronary syndrome (ACS) are at risk especially in the period shortly after the event. Alterations in respiratory control have been associated with adverse prognosis. The aim of our study was to assess if the nocturnal respiratory rate (NRR) is a predictor of mortality in patients with ACS presenting in the emergency department.

Methods Clinically stable consecutive patients with ACS aged ≥ 18 years were prospectively enrolled. The Global Registry of Acute Coronary Events (GRACE) score and left ventricular ejection fraction (LVEF) were assessed for all patients. The average NRR over a period of 6 hours was determined by the records of the surveillance monitors in the first night after admission. Primary and secondary endpoints were intrahospital and 2 years all-cause mortality, respectively.

Results Of the 860 patients with ACS, 21 (2.4%) died within the intrahospital phase and 108 patients (12.6%) died within the subsequent 2 years. The NRR was a significant predictor of both endpoints and was independent from the GRACE score and LVEF. Implementing the NRR into the GRACE risk model leads to a significant increase of the C-statistics especially for prediction of intrahospital mortality.

Conclusion The NRR is an independent predictor of mortality in patients with ACS.

Key messages

What is already know about this subject?
► Previous studies indicate that alterations in respiratory control predict mortality in postinfarction patients.

What does this study add?
► We tested if assessment of the nocturnal respiratory rate (NRR) obtained from routine surveillance monitors immediately after the index event enables a quick and early risk stratification in a large population of all-comers with ACS presenting in the emergency department.

How might this impact on clinical practice?
► The assessment of NRR offers additional prognostic information in patients with ACS for the prediction of mortality.
► This information was obtained with a simple, inexpensive, quick and readily available technology which could be easily implemented in existing monitoring devices.

INTRODUCTION

Patients with acute coronary syndrome (ACS) are at most risk of mortality during in the first days after the event. All patients with ACS should therefore undergo early risk stratification to identify candidates who are likely to benefit from an intensified treatment and monitoring. Currently, identification of high-risk patients is based on the finding of a reduced left ventricular ejection fraction (LVEF) or by applying score systems such as the GRACE (Global Registry of Acute Coronary Events) risk score.[1 2] However, risk stratification of unselected patients with ACS by LVEF <30% can only identify a minor part of patients who die after the ACS and the GRACE risk score has its value especially in patients with non-ST-elevation myocardial infarction (NSTEMI).[1 2]

Experimental and clinical studies indicate that in patients with cardiovascular diseases important prognostic information can be derived from the functional status of the cardiac autonomic nervous system. In the setting of acute myocardial infarction, loss of vagal activity has been linked to increased mortality risk.[3 4] Also the respiratory rate is strongly modulated by the autonomic nervous system. Previous studies indicate that alterations in respiratory control predict mortality in postinfarction patients.[5 6]

In the present study, we tested if assessment of the nocturnal respiratory rate (NRR) obtained from routine surveillance monitors immediately after the index event enables a quick and early risk stratification in a large population of all-comers with ACS presenting in the emergency department.

METHODS

Participants

Consecutive patients≥18 years were prospectively enrolled between November 2010 and December 2012 having been admitted to the emergency department (which includes the Chest Pain Unit) of the University of Tübingen, Germany, with ACS. ACS was defined as either presence of ST-elevation myocardial infarction (STEMI), NSTEMI or unstable angina pectoris (UAP) according to current guidelines.[7–10] Clinically unstable patients with cardiogenic shock who required invasive or non-invasive mechanical ventilation were admitted directly to the intensive care unit and were not included in our study.[11]

Assessment of NRR

Patients were monitored (DASH 4000, General Electrics, Fairfield, Connecticut, USA; sample frequency, 100 Hz) for a period of at least 48 hours. Monitoring was performed under routine clinical conditions at the intensive coronary care unit, after performing the acute medical care in the emergency room and catheter lab. The ECG channel of the surveillance monitors was stored on a central server. The respiratory rate was extracted from the ECG recording. Technical details of the methodology of assessment of the respiratory rate from ECG recordings have been described elsewhere.[12] To calculate the average NRR, the period from 0:00 to 6:00 from the first night after complete admission was used. In addition, we calculated the NRR from shorter recordings, after just 1 hour (0:00 to 01:00) and 2 hours (0.00 to 02.00).

Assessment of LVEF

The LVEF was determined directly on admission of the patient either by transthoracic echocardiography by the biplane Simpson's method or by left ventriculography in patients who were transferred immediately to the cath lab.

Assessment of the GRACE score

The GRACE score including age, systolic blood pressure, heart rate, Killip classification, serum creatinine, cardiac arrest at admission, ST-segment deviation and cardiac biomarkers was calculated as previously described.[2]

Study endpoints and follow-up

The primary study endpoint was the intrahospital all-cause mortality. The secondary endpoint was 2-year all-cause mortality. Intrahospital deaths were assessed via the electronic hospital information system. For assessment of 2-year mortality, patients were contacted by telephone. Two-year follow-up information was available in 95.9% of the patients. Patients lost to follow-up were censored at the time of last contact.

Statistical analyses

Continuous variables are presented as median and IQRs and were compared using the Mann-Whitney U test after performing a normality test (Kolmogorov-Smirnov test). Qualitative data are expressed as percentages and were analysed using the χ^2 test. Receiver Operating Characteristic (ROC) curves were constructed for risk predictors by plotting 1 − specificity versus sensitivity. ROC curves were quantified by the area under the curve (AUC). To test the difference between ROC curves, bootstrapping was employed based on the creation of pseudo-replicate datasets by random resampling of the dataset n times for error estimation (n=1000 in this study). The association of risk variables with the endpoints was tested by univariable and multivariable logistic and Cox-regression analyses. Multivariable analyses included NRR as well as the GRACE score and the LVEF. In the analysis for the 2-year mortality, female gender and diabetes were also taken into account. To test the incremental prognostic value of NRR on top of the GRACE risk model, we implemented C-statistic, continuous NRI and the integrated discrimination improvement (IDI) score. Mortality rates were estimated by the Kaplan-Meier method. HRs were presented with 95% CIs. When used as categorical variable, the NRR was dichotomized at the cut-off value of 16.8 breaths/min. The cut-off value was determined by a method described by Youden et al.[13] Differences were considered statistically significant when p value was <0.05. Statistical analyses were performed using CRAN R V.3.0.1 and SPSS V.21.0.

RESULTS

During the recruitment period, 860 patients with ACS were prospectively included. Table 1 shows the patients' characteristics. Mean age was 69.7 years, 34.8% of the patients were female. In 135 patients (15.7%) had STEMI, 312 (51.2%) had NSTEMI and 285 (33.1%) suffered from UAP. During NRR recording, 86% of patients were in sinus rhythm.

Twenty-one patients (2.4%) died during the hospital stay. All patients who experienced intrahospital death died due to a cardiovascular reason. In total, 108 patients (12.6%) died within 2 years after the index event. The NRR was significantly higher in patients who died during the hospital phase or within the subsequent 2 years than in survivors (18.0 (3.9) breaths/min vs 15.3 (2.4) breaths/min and 16.9 (3.7) breaths/min vs 15.2 (2.2) breaths/min, respectively, p<0.001 for both). Significant differences were also noted for the GRACE score for the primary and secondary endpoint, respectively, and for LVEF (table 2). In addition, patients who died within the hospital stay were significantly older and were more likely to suffer from renal insufficiency. Patients who died within the subsequent 2 years after NRR assessment were of higher age, were more often diabetics, had an impaired renal function and were more often females.

The NRR yielded AUCs of 0.806 (95% CI 0.725 to 0.887) and 0.676 (0.616–0.736) for the primary and secondary endpoints, respectively (p<0.001 for both, figure 1). Figure 2 shows cumulative mortality rates of patients stratified by NRR. The 206 patients with NRR

Table 1 Clinical characteristics and outcomes of the study cohort

Variable	Study population (n=860)
Age (years)	72.0 (18.0)
Female	299 (34.8%)
Left ventricular ejection fraction (%)	50.0 (20.0)
Medical history	
Myocardial infarction	270 (31.4%)
Congestive heart failure	216 (25.1%)
Atrial fibrillation	195 (22.7%)
Stroke	87 (10.1%)
Peripheral arterial disease	123 (14.3%)
Chronic renal insufficiency	181 (21%)
Percutaneous coronary intervention	223 (25.9%)
Coronary artery bypass graft	86 (10%)
Arterial hypertension	714 (83.0%)
Diabetes mellitus	270 (31.4%)
Hyperlipidaemia	406 (47.2%)
Smoking	333 (38.7%)
Family history of coronary artery disease	218 (25.3%)
STEMI	135 (15.7%)
NSTEMI	312 (51.2%)
UAP	285 (33.1%)
In-hospital coronary angiography	794 (92.3%)
In-hospital percutaneous coronary intervention	780 (90.7%)
Intrahospital mortality	21 (2.4%)
2-years mortality	108 (12.6%)

Chronic renal insufficiency, GFR < 90 mL/min; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.

≥16.8 breaths/min had an adverse prognosis with a 2-year mortality rate of 27.2% while the 654 patients with NRR <16.8 breaths/min had a significantly better prognosis with a 2-year mortality rate of only 8.0% (p<0.001 for overall difference).

We also calculated the NRR from shorter recording intervals. For 1 hour the NRR was also significantly higher in patients who died during the hospital phase or within the subsequent 2 years than in survivors (16.7 (2.7) breaths/min vs 14.5 (2.4) breaths/min and 16.0 (3.5) breaths/min vs 14.4 (2.3) breaths/min, respectively, p<0.001 for both). The AUC was 0.781 and 0.668 for the primary and secondary endpoints.

For 2 hours the NRR was also significantly higher in patients who died during the hospital phase or within the subsequent 2 years than in survivors (16.5 (3.0) breaths/min vs 14.5 (2.3) breaths/min and 15.9 (3.5) breaths/min vs 14.4 (2.2) breaths/min, respectively, p<0.001 for

both). The AUC was 0.787 and 0.664 for the primary and secondary endpoints.

In our cohort, 449 of the 860 patients underwent percutaneous coronary intervention (PCI) before NRR assessment, 331 patients underwent PCI in the period after the NRR assessment and 80 patients did not undergo PCI. Significantly higher NRR values can be seen in non-survivors of all subgroups except for the patients without PCI with regard to 2-year mortality. Especially in patients treated by PCI after NRR assessment (331 patients, two intrahospital deaths), the NRR showed a very good C-statistic with an AUC of 0.977 regarding the intrahospital mortality (table 3).

In a further subgroup analysis, we investigated the NRR in patients with STEMI, NSTEMI and UAP. In all subgroups, except for the 2-year mortality in patients with UAP, non-survivors show significantly higher NRR values compared with survivors (table 4).

Table 5 shows univariable and multivariable analyses of NRR, the GRACE score and LVEF for prediction of both endpoints. NRR proved to be an independent risk factor yielding a HR of 1.35 (95% CI 1.09 to 1.68, p=0.006) for intrahospital mortality and 1.15 (95% CI 1.05 to 1.26, p=0.002) for 2-year mortality, respectively. Implementing NRR into the GRACE risk model led to a significant increase of the C-statistics for prediction of intrahospital mortality from 0.842 (95% CI 0.740 to 0.944) to 0.876 (95% CI 0.790 to 0.961; p=0.02 for difference, continuous NRI 0.556, p=0.01, IDI 0.022: p<0.01, figure 3A). For prediction of 2-year mortality only the continuous NRI showed significant improvement from 0.776 (95% CI 0.731 to 0.822) to 0.784 (95% CI 0.737 to 0.830; p=0.95 for difference, continuous NRI 0.313, p<0.01, IDI 0.0175; p=0.286, figure 3B).

DISCUSSION

The present study shows that the average NRR during the first night following hospital admission provides powerful prognostic information regarding intrahospital mortality in all-comers with ACS presenting in the emergency department. The prognostic value is independent from established risk predictors such as the GRACE score and LVEF. In addition, the NRR significantly improved the GRACE risk model. Regarding 2-year mortality, NRR also proved to be an independent risk factor but only improved the GRACE risk model to a weaker extent.

Current guidelines recommend monitoring of patients with ACS as these patients are at substantial risk of death due to malignant arrhythmias, reinfarction or progressive heart failure.[14] Some patients, however, are likely to benefit from an intensified treatment and monitoring. The identification of high-risk patients at an early stage after admission would be of great clinical interest. Established methods for risk assessment in patients with ACS are clinical risk scores such as the GRACE score or LVEF.[1 2 15] However, prognostic evaluation using these approaches has limitations and risk markers complementary to the

Table 2 Characteristics of survivors and non-survivors of the intrahospital phase

	IHM			2YM		
	Survivors (n=839)	Non-survivors (n=21)	P values	Survivors (n=752)	Non-survivors (n=108)	P values
Age (years)	72.0 (18.0)	81.0 (12.0)	0.002	71.0 (18.0)	80.0 (11.0)	<0.001
Female	290 (34.6%)	9 (42.9%)	0.488	247 (32.8%)	52 (48.1%)	0.002
GRACE score (points)	122 (44)	182 (40)	<0.001	119 (43)	157 (50)	<0.001
LVEF (%)	50 (20)	30 (25)	0.005	50 (20)	40 (25)	<0.001
Diabetes mellitus	261 (31.1%)	9 (42.9%)	0.245	218 (29.0%)	52 (48.1%)	<0.001
Renal insufficiency	170 (20.3%)	11 (52.4%)	<0.001	135 (18.0%)	46 (42.6%)	<0.001
NRR (breaths/min)	15.3 (2.4)	18.0 (3.9)	<0.001	15.2 (2.2)	16.9 (3.7)	<0.001

GRACE, Global Registry of Acute Coronary Events; IHM, intrahospital mortality; LVEF, left ventricular ejection fraction; NNR, nocturnal respiration rate; 2YM, 2-year mortality.

established methods are warranted. The optimal risk marker would be easily and quickly determinable, inexpensive, without demands on technical equipment or on patient cooperation.[16] Most of these requirements apply to the NRR: the determination of NRR can be carried out using most surveillance monitors and without additional expense. The nocturnal determination off NRR allows standardised test conditions, also without any extra effort and without specific patient cooperation.

The NRR can be assessed by different methods through routine surveillance monitors. In this study, the respiratory rate was calculated from the ECG channel because not all surveillance monitors support other methods of respiration rate assessment.[12] This method is therefore applicable to monitoring stations with basic technical equipment. Since all patients with ACS require monitoring especially in the first 24–48 hours,[14] the determination of NRR could be integrated into routine clinical practice without significant additional expense.

We were able to show that the average NRR during the first night after admission provides additional prognostic information, especially with respect to the intrahospital mortality. On the long term, the NRR might therefore be helpful for clinical decisions such as prolonged monitoring and intensified medical, interventional and device-based treatment of high-risk patients with ACS.

Since the time of revascularisation can have a considerable effect on NRR and on outcome, we have carried out subgroup analyses of patients who underwent PCI before NRR assessment, patients who underwent PCI after NRR assessment and patients who did not undergo PCI. A significantly higher NRR can be seen in the non-survivors of all subgroups except for patients without PCI with regard to 2-year mortality. A very good C-statistic was found for patients in whom the NRR was assessed prior to revascularisation with regard to intrahospital mortality. These patients might have benefited from an earlier invasive diagnosis and therapy. However, the low event rate in this subgroup only allows to draw this conclusion to a limited extent.

The fact that the respiratory rate provides prognostic information in postinfarction patients has already been shown in other studies.[5 17 18] The NRR seems to be particularly suitable because of its assessment under standardised conditions in the night compared with daytime measurements.[6] Other studies used standard 24-hour
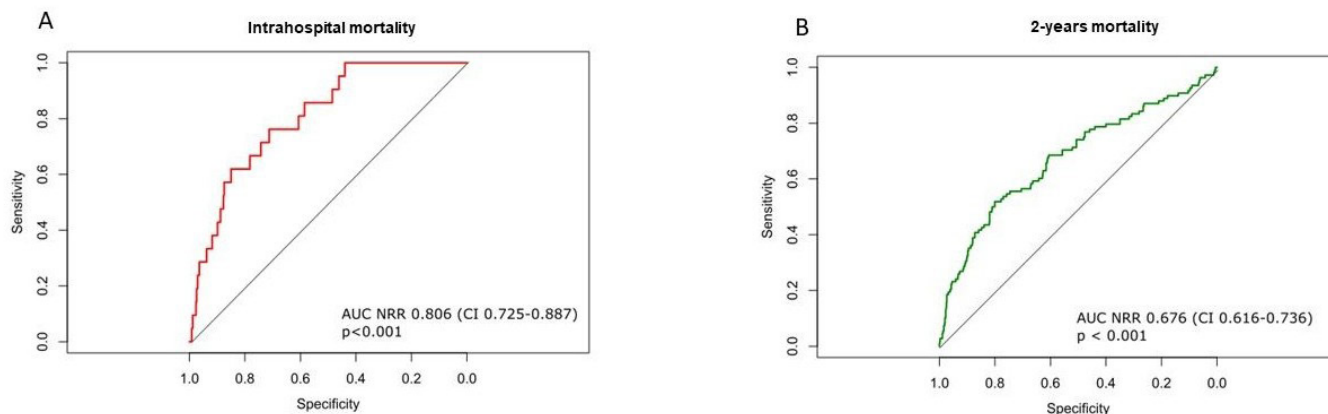

Figure 1 Receiver-operator characteristic curves for prediction of the primary and secondary endpoint by the nocturnal respiratory rate (NNR) in patients with acute coronary syndrome. AUC, area under the curve.
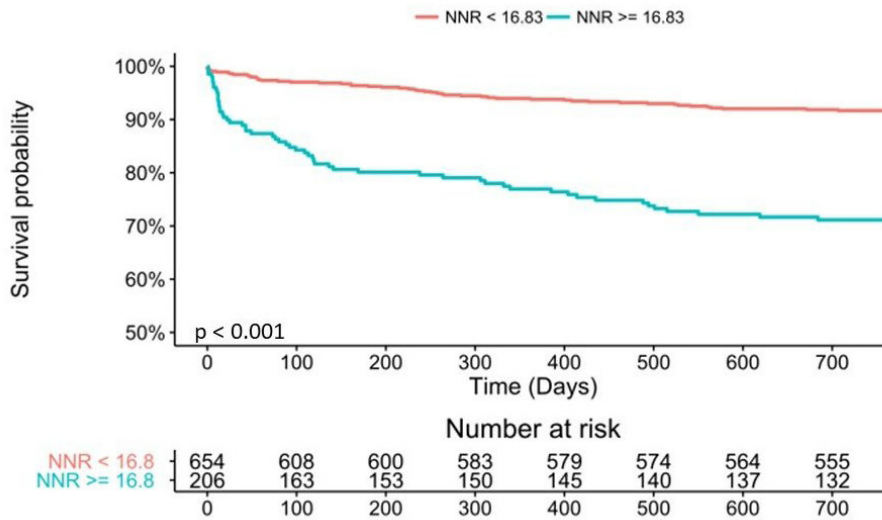
Figure 2 Cumulative mortality rate of patients stratified by the nocturnal respiratory rate (NNR) <16.8 breaths/min and ≥16.8 breaths/min, respectively.

Holter recordings or short records of 10 min respiratory rate at rest within an extended period for prediction of mortality after myocardial infarction.[5 6 17] The difference of our study is first that we have determined the NRR in the routine clinical setting of the emergency department via standard patient monitors without any additional diagnostic tools. Second, the time of NRR assessment is clearly defined in our study, that is, the first night after hospital admission. Thus, by the presented setting objective prognostic information can be obtained shortly after the clinical event, which can be useful in addition to other risk factors for immediate planning of further treatment of the individual patient. Third, other studies have assessed an association between respiratory rate and post-MI prognosis. We have focused on a broader spectrum of all-comers with ACS including patients with UAP.

The respiratory rate is strongly influenced by the balance of the autonomic nervous system. Increased respiratory rate at admission may therefore by a sign of altered autonomic control of respiratory activity due

Table 3 Subgroup analysis depending on the time of therapy and the modality of therapy

Treatment	IHM	N	NRR	P values	AUC	2YM	N	NRR	P values	AUC
No PCI	No	71	15.8±1.7	<0.001	0.837	No	58	15.9±1.7	0.228	0.588
	Yes	9	18.3±1.9			Yes	22	16.6±2.2		
PCI before NRR assessment	No	439	15.5±1.9	0.007	0.748	No	401	15.4±1.8	<0.001	0.704
	Yes	10	17.1±1.8			Yes	48	17.1±2.5		
PCI after NRR assessment	No	329	15.5±2.1	0.02	0.977	No	293	15.4±2.1	<0.001	0.665
	Yes	2	20.4±0.4			Yes	38	16.8±2.6		

AUC, IHM, intrahospital mortality; NRR, nocturnal respiration rate; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris; 2YM, 2-year mortality.

Table 4 Subgroup analysis depending on the type of ACS

ACS group	IHM	N	NRR	P values	AUC	2YM	N	NRR	P values	AUC
STEMI	No	131	15.5±1.8	0.018	0.847	No	120	15.4±1.6	0.006	0.717
	Yes	4 (3.0%)	17.6±1.3			Yes	15 (12.5%)	16.9±12.5		
NSTEMI	No	424	15.9±2.1	<0.001	0.747	No	367	15.8±2.0	<0.001	0.675
	Yes	16 (3.7%)	17.9±2.1			Yes	73 (19.9%)	17.2±2.4		
UAP	No	284	15.0±1.8	0.007	1.000	No	265	15.0±1.8	0.266	0.575
	Yes	1 (0.3%)	20.6			Yes	20 (7.5%)	15.6±2.4		

AUC, area IHM, intrahospital mortality; NRR, nocturnal respiration rate; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris; 2YM, 2-year mortality.

Table 5 Univariable and multivariable binary logistic regression and Cox regression analysis for prediction of intrahospital mortality and 2-year mortality

IHM

Variable	Univariable binary logistic regression			Multivariable binary logistic regression		
	HR (95% CI)	Wald	P values	HR (95% CI)	Wald	P values
GRACE score	1.04 (1.03 to 1.06)	34.7	<0.001	1.04 (1.02 to 1.68)	20.0	<0.001
NRR (breaths/min)	1.63 (1.34 to 1.98)	24.1	<0.001	1.35 (1.09 to 1.68)	7.5	0.006
LVEF (%)	0.94 (0.90 to 0.98)	10.1	0.002	0.98 (0.94 to 1.02)	1.1	0.298

2YM

Variable	Univariable Cox regression			Multivariable Cox regression		
	HR (95% CI)	Wald	P values	HR (95% CI)	Wald	P values
GRACE score	1.03 (1.02 to 1.03)	113.9	<0.001	1.02 (1.02 to 1.03)	53.8	<0.001
Female	1.80 (1.23 to 2.6)	9.1	0.02	0.86 (0.70 to 1.04)	2.4	0.123
NRR (breaths/min)	1.35 (1.24 to 1.47)	50.0	<0.001	1.15 (1.05 to 1.26)	9.9	0.002
LVEF (%)	0.94 (0.93 to 0.96)	50.7	<0.001	0.97 (0.95 to 0.98)	13.6	<0.001
Diabetes mellitus	0.48 (0.33 to 0.71)	14.21	<0.001	0.62 (0.43 to 0.91)	6.0	0.014

GRACE, Global Registry of Acute Coronary Events; IHM, intrahospital mortality; LVEF, left ventricular ejection fraction; NNR, nocturnal respiration rate; 2YM, 2-year mortality.

to enhanced sympathetic activity and vagal withdrawal in ACS and also maybe due to progressive pulmonary congestion.[4] Other parameters evaluating the function of the autonomic nervous system, such as various parameters of heart rate variability, are also strong risk predictors in patients with ACS.[4 19–22] For assessment of these parameters, however, the presence of sinus rhythm is mandatory which is not needed for determination of NRR.

The limitations of our study need to be recognised. First, we cannot compare the prognostic information of NRR with parameters of heart rate variability since the study cohort includes patients with atrial fibrillation. However, as atrial fibrillation in patients with ACS is often prevalent, risk stratification by NRR which can be performed irrespective of the patient's heart rhythm is favourable. Second, the presence of motion artefacts and other technical failures could affect the determination

of the respiratory rate from the ECG channel. Further underlying respiratory pattern could affect the NRR. The calculation of the average respiratory rate over a period of 6 hours, however, should reduce the influence of corresponding disturbances. The choice of the period from 0:00 to 6:00 was due to the consideration that during this time the patient is most likely asleep; however, there was no monitoring of the sleep state. However, we consider that the chosen nightly episode is the optimal time for the standardised determination of the respiratory rate since the external influences are the lowest at this time. We also calculated the NRR from shorter recording intervals (1 and 2 hours). Again, there were highly significant differences with respect to both endpoints. However, the respective C-statistic was better with a longer recording time (6 hours). We interpret this by the fact that disturbances have less effects with longer recording time. In
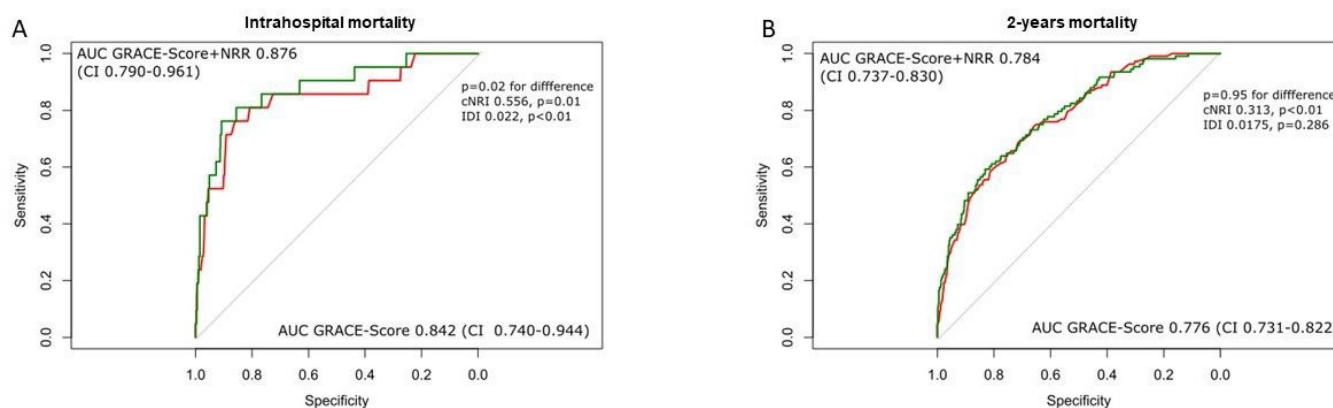

Figure 3 Receiver-operator characteristic curves for prediction of the primary and secondary endpoint in patients with acute coronary syndrome. (A, B)The GRACE score as well as the combination of the GRACE score and the nocturnal respiratory rate (NRR). AUC, area under the curve.

addition, specific respiratory disorders that may affect the results are also better detected with longer recording time.

Third, the selected cut-off for NRR of 16.8/min was determined retrospectively and was not derived from pathophysiological reasoning or previous literature data. Fourth, ACS is composed of multiple types of infarction and ischaemia which have variable effects on heart and vascular baroceptors and chemoceptors and finally also on the NRR. However, we performed subgroup analyses on patients with STEMI, NSTEMI and UAP and non-survivors of all ACS subsets presented with significantly higher NRR values except patients with UAP who died within 2 years. Fifth, we cannot provide systematic information about the exact time of the onset of ACS and with regard to drugs given in the first hours of ACS which both may have an effect on NRR. Sixth, LVEF was assessed by echocardiography or by left ventriculography. However, studies report a sufficient correlation of both modalities to assess LVEF.[23]

Finally, further studies are needed to show that incorporation of the NRR into the risk stratification of patients with ACS and clinical decision-making contributes to an improved prognosis.

CONCLUSIONS

The NRR is an independent predictor of intrahospital mortality in patients with ACS. The assessment of NRR offers additional prognostic value to GRACE score and LVEF in patients with ACS for the prediction of in-hospital mortality. This information was obtained with a simple, inexpensive, quick and readily available technology which could be easily implemented in existing monitoring devices.

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