Association between High Cumulative Numbers of Elevated Heart Rate and Mortality in Neurological ICU patients: Retrospective Analysis of eICU Collaborative Research Database

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Research article

Keywords: eICU-CRD, NICU, heart rate, APACHE IV score, mortality

Posted Date: April 22nd, 2019

DOI: https://doi.org/10.21203/rs.2.9183/v1

Abstract

Background Heart rate is routinely measured in Neurological intensive care unit(NICU), but its prognostic value remains debated. We sought to evaluate the association of high cumulative numbers of elevated Heart Rate (HcneHR) with mortality in NICU patients. Methods We used a large observational eICU Collaborative Research Database (eICU-CRD), where continous heart rate monitoring every 5 minute was available. We collected periodic heart rate, disease severity (APACHE IV score), NICU and hospital mortality and other information in 8347 patient admissions from the eICU-CRD. The cumulative numbers of Heart Rate (cneHR) were defined as >100 beats/min in first admittion 24 hours, and if cneHR ≥10,then was defined as higt cneHR(HcneHR). The primary outcome was NICU mortality. The other outcomes were hospital mortality, length of NICU stay and APACHE IV score. Multivariable logistic regression was used to assess for association for HcneHR and other covariance with NICU and hospiltal discharge status. Results The mean age of patients were 63 years, and the most frequent disease categories of NICU in eICU-CRD were postoperation (25%), stroke(19%), traumatic brain injury(14%). The mean APACHE IV score was 50. Overall NICU mortality of the cohort at discharge was 4%, and hospital mortality was 8%. The NICU mortality of HcneHR patients was 7%. Adjusted logistic regression for HcneHR showed a significantly increased risk of NICU death with odds ratio 1.61(confidence interval, 1.26-2.06; P <0 .001). Conclusions In adult neurocritically ill patients, we found a significant association for HcneHR with elevated mortality and several others important patient-centered outcomes.

Background

The burden of critical illness is higher than generally appreciated and will increase as the population ages, preventive and therapeutic interventions that are generalisable across ICUs are needed[1]. Heart rate is routinely measured in ICU but its prognostic value remains debated. It is well known that critically ill patients are prone to develop tachycardia due to various conditions such as anxiety, pain, fever, infection, hypovolemia, exaggerated sympathetic activation, heart failure, hypoxia, anemia, drug effects, primary arrhythmia and so on[2-4]. It has been shown that there is an association for high heart rate(HR) and poor outcomes in critically ill patients[5], and HR is an important part of most ICU prognosis scores[6].

The critical care unit is a dataintensive environment[7]. However, as yet, heart rate from bedside monitor in critical care is evaluated by clinicians almost in much the same way as before, little information is available on the critical duration of tachycardia, especially in neurological intensive care unit(NICU), which focuses on the optimal management of acutely ill patients with life threatening neurologic and neurosurgical disease or with life-threatening neurologic manifestations of systemic disease[8]. We may get more information on the continuous heart rate monitoring.

Therefore, in this study, we hypothesized that an elevated HR of >100 beats/min for a prolonged period, where we showed it as high cumulative numbers of elevated HR(HcneHR) during the first day of NICU stay, may be associated with decreased survival in neurocritically ill patients. This may help clinicians to better identify high risk patients admitted in NICU.

Methods

Setting

This study used data stored in the high-resolution database, the eICU-CRD(eicu-crd.mit.edu), which comprises 200,859 patient unit encounters for 139,367 unique patients admitted between 2014 and 2015. The database contains parameters that were available in the ICU clinical information system, including vital signs, laboratory measurements, medications, APACHE components, care plan information, admission diagnosis, patient history, time-stamped diagnoses and similarly chosen treatments. The elaborate description of eICU-CRD is available elsewhere[9].

The eICU-CRD was exempt from institutional review board(IRB) approval due to the retrospective design, lack of direct patient intervention, and the security schema, for which the re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219-2). Due to the HIPAA compliant de-identification in this database, our institutional IRB requirement was waived. After completing a National Institutes of Health(NIH) web-based training course(Protecting Human Research Participants), the author(dw zhou, certification number: 28795067) was approved to access to the database for research aims.

Study Population

All patients in the eICU-CRD were eligible for inclusion in the present investigation. As for those who admitted in NICU for more than once, we considered them as different patients. We selected all adults patients admitted in NICU with length of stay >24 hours, and excluded those who used heart rate controlling drug during the first day in NICU. Heart rate controlling drug contained β-blocker and calcium antagonist. We collected all periodically recorded heart rates for the first 24hours of NICU admission, and patients without periodical heart rate data were excluded. Patients without APACHE IV score, pulse oxygen saturation(SpO2), admission temperature, admission blood pressure, gender information were excluded.

Clinical Variables and Outcomes

Data on the following information during the first 24 hours of admission were extracted: age, gender, ethnicity (caucasian, african american, hispanic, asian, ative american, other/unknown), admission disease categories (postoperation, ischemic stroke, traumatic brain injury, intracranial hemorrhage, seizures, sepsis, subarachnoid hemorrhage, coma, others), admission vital sign(temperature, respiratory rate, heart rate, mean blood pressure, SpO2), heart rate related indexes for continuously periodical monitoring(cneHR, HcneHR, maximum heart rate, minimum heart rate, average heart rate), acute physiology score, APACHE IV score, the first day hemoglobin, comorbidities, including atrial fibrillation, cardiovascular diseases, tracheal intubation, mechanical ventilation, vasopressors, length of NICU stay, the NICU and hospital discharge status(alive or expired). All patients admitted from the operating room or

recovery room had a surgical diagnosis, even though some surgical patients had a medical reason for admission to the NICU.

Periodical data refers to data which is consistently interfaced from bedside vital signs monitors into eCareManager. Continuously measured heart rate was originally collected at 1-minute intervals, with 5-minute medians archived in eICU-CRD. That is to say, every patient in the first day of NICU had 288 heart rate values. The cneHR was defined as cumulative numbers of heart rate >100 beats/min in first admission 24 hours archived in eICU-CRD “vitalPeriodic” table, and if cneHR (10,then was defined high cneHR(HcneHR), and cneHR<10 was defined as Low cneHR(LcneHR).

The primary endpoint of our study was NICU mortality, defined as death observed during NICU stay. Other study endpoints included hospital mortality, NICU length of stay and APACHE IV score. NICU length of stay was defined as the difference between date of NICU admission and discharge.

Statistical Analysis

Continuous variables are shown as mean (standard deviation) or median (interquartile range), and were analyzed with Wilcoxon rank-sum tests. For dataset with a large sample size, the Anderson-Darling test can be very sensitive to a small deviation from the normal distribution. So we switched off the normality testing and still used mean and standard deviation to describe the data[10]. Categorical variables were reported as numbers and percentages, and were analyzed with chi-square test. As for missing data onto the first day hemoglobin, we use the mean hemoglobin of the NICU alive patients to imputed the missing data onto the NICU alive patients, so was for the NICU expired patients. Some patients did not get the heart rate monitoring immediately after admission to NICU, the missing heart rate data were replaced using next observation carried backward(NOCB) method.

Receiver operating characteristic (ROC) analysis was used to evaluate the predictive ability of cneHR. The best cut-off value was determined using the Youden index, and was used to defined HcneHR. Uadjusted crude outcomes including NICU mortality, hospital mortality, NICU length of stay and APACHE IV score were compared between HcneHR and LcneHR patients.

Logistic regression model was fitted to adjust to odds ratio of NICU and hospital mortality. Three models were created: model 1 adjusted to APACHE IV score; model 2 adjusted for demographics and APACHE IV score; model 3 adjusted for model 2 covariance plus disease categories, admission vital sign(temperature, respiratory rate, heart rate, mean blood pressure,SpO2), the first day hemoglobin, use of mechanical ventilation, use of vasopressors, length of NICU stay, comorbidities, including atrial fibrillation, cardiovascular diseases. A stepwise backward elimination method with a significance level of 0.05 was used to build the final model.

We determined the predictive efficacy of HcneHR in conjunction with currently accepted known risk factors for mortality. Here wo chosen APACHE IV score, use of mechanical ventilation, HcneHR and use of vasopressors to construct prediction model for NICU expired, and showed it in nomogram with R package

“rms”. Each variable was represented by a bar. A given value of a variable can be mapped to the point bar at the top of the graph and there is a point value for that given value. After each variable was assigned to a point number, they were summed and mapped to the total point bar. Then there will be a value in the “Risk of NICU Expired” bar corresponding to those total points. ROC analysis was used to evaluate the predictive ability of the predictive model. For disease subgroup analysis, we used model1 to calculate odds ratio of NICU and hospital mortality for different diseases, and showed them with forest graph.

Data extraction was performed using PostgreSQL (version 10.5, www.postgresql.org) and pgADmin PostgreSQL tools(version 4). R (version 3.5.1, www.r-project.org) was used for statistical analysis. A two-sided P value of <0.05 was considered statistically significant.

Results

Patient Characteristics

The eICU-CRD contained 200,839 patients, including 14,451 NICU patients. Of the remaining 14,451 patients, we excluded those with length of stay (24h, age<18, and those who used heart rate controlling drug. A total of 8,347 patients met our inclusion criteria after excluding those with missing data(Fig 1), of which 339 were expired when discharged from NICU, giving an NICU mortality rate of 4%. Demographics and baseline characteristics between alive and expired patients are presented in Table 1. The mean age were 63 years, and most patients ethnicity were “Caucasian” (75%). The main disease categories were postoperative patients (25%) , stroke(19%), traumatic brain injury(TBI)(14%) , intracranial hemorrhage(10%), and so on. The mean APACHE IV score was 50. On the first 24hours, cneHR was significantly higher in NICU expired patients than in alive patients(72.5±91.58 vs. 34.26±65.39; p<0.001), also in hospital expired and alive patients(71.41±90.8 vs. 50.52±73.18; p<0.001)(supplementary fig.1). The number of missing data onto hemoglobin was 1127(13.5%).

HcneHR and the Outcome Analysis

Table 2 showed crude outcomes by cneHR category. Patients with HcneHR had significantly higher NICU and hospital mortality. ROC analysis showed area under curve(AUC) of the predictive ability of cneHR was 0.655, and the best cut-off point was 9.5(supplementary fig.2), that is why we chosen 10 as the cut-off point of HcneHR and LcneHR. The percentage of HcneHR in NICU expired patients was 61%, while the alive one was 36%. Fig.2 showed the different percentage of HcneHR between NICU alive and expired patients over time. The length of NICU stay and APACHE IV score were significantly different between the HcneHR and LcneHR patients(table 2).

Contribution of HcneHR and other covariance to Mortality

Table 3 showed the ORs of NICU and hospital mortality in the different logistic regression models. The unadjusted OR of HcneHR for NICU mortality was 2.84(2.27-3.55, p<0.001). After adjustment for demographics , APACHE IV score and other clinical parameters, the OR decreased but remained

statistically significant for HcneHR patients. As for subgroup analysis of different diseases, in a univariable logistic regression, HcneHR significantly associated with NICU mortality in postoperation, ischemic stroke, traumatic brain injury, intracranial hemorrhage and others groups. Furthermore, after APACHE IV score was adjusted to a multivariable logistic regression analysis, HcneHR remained significantly associated with NICU mortality in ischemic stroke, intracranial hemorrhage and others groups(fig.3), and significantly associated with hospital mortality in traumatic brain injury, intracranial hemorrhage and others groups (supplementary fig.3).

Fig.4 showed the nomogram of predictive model for prediction of the death risk for NICU patients. The predictive model used APACHE IV score, mechanical ventilation, vasopressors and HcneHR as covariance. ROC analysis of this predictive model showed AUC was 0.855, as showed in supplementary fig.3.

In a post hoc analysis, we explored the ORs of different heart rate and corresponding cneHR. We calculated the adjusted odds ratio of death using a minimally adjusted logistic regression model (including age, gender, and ethnicity) for each combination of cumulative numbers and heart rate thresholds. The results were shown in Figure 5, where each square showed the corresponding odds ratio of NICU death numerically. There was an increasing trend of OR as the heart rate and cneHR increased.

Discussion

In this analysis of a large and heterogeneous NICU clinical database, we found a significant association for HcneHR with elevated NICU mortality, hospital mortality, ICU length of stay and APACHE IV score. As cneHR can be readily got from the ECG monitoring system, which is common in NICU, it may be a good tool to better identify high risk patients admitted in NICU. In contrast to other heart rate parameters, cneHR integrates many parameters, like elevated heart rate, volatility and duration.

Elevated resting heart rate (RHR) is associated with all cause mortality in the general population[11, 12], and lower RHR is related to lower all-cause mortality[13]. Elevated preoperative HR is associated with impaired cardiopulmonary performance consistent with clinically unsuspected, subclinical cardiac failure, and is associated with myocardial injury, myocardial infarction, and mortality after non-cardiac surgery[14, 15]. In critically ill patients, prolonged elevated HR increased incidence of major cardiac events and was associated with a significantly longer ICU stay and reduced survival[5, 16]. Our findings are in line with these studies.That is to say, in critically ill patients admitted in NICU, HcneHR was associated with NICU and hospital mortality. In the time series characteristics of HcneHR percentage, the NICU alive patients had a gradually downward trend, and tended to be stable after 12 hours. However, the HcneHR percentage of NICU expired patients was higher, and jumped over time(Fig.2).

The disease profile of our study contained surgical diagnosis, ischemic stroke, traumatic brain injury,intracranial hemorrhage, seizures, sepsis, subarachnoid hemorrhage, coma, and others groups. There are a number of studies which have evaluated the association for increased HR and mortality in neurocritical patients. Preoperative elevated heart rate is associated with mortality after neurosurgery[15].

In moderate and severe TBI patients, a correlation between elevated baseline HR and 60th-day mortality was shown[17]. After SAH, prolonged elevated HR was associated with 3-month poor outcome and an increased hazard for delayed cerebral ischemia, myocardial injury and pulmonary edema[18]. Among intracerebral hemorrhage and ischemic stroke patients, higher admission HR was independently associated with death and poor functional outcome[19, 20]. Elevated HR prior to partial seizure onset of those attacks which become secondarily generalized compared to seizures which remain localized, and this may be relevant to the understanding of sudden death in epilepsy[21]. In our study, subgroup analyses showed HcneHR were associated with NICU mortality in ischemic stroke, intracranial hemorrhage and others groups, and significantly associated with hospital mortality in traumatic brain injury, intracranial hemorrhage and others groups.

There are myriad causes of elevated HR in neurological critically-ill patients, however, including but not limited to pain, agitation, hypovolemia, infection, fever and systemic inflammation, or vasoactive therapy with vasopressors,and multiple potential causes may coexist, making it difficult or impossible to get a precise cause[2-4]. Elevated HR can increase metabolic oxygen demand, increase blood pressure from increased sympathetic activity, activate inflammatory pathway, or cause endothelial dysfunction[22, 23]. The precise mechanism between elevated HR and poor outcome still remain difficult to unravel.

This was an observational analysis and therefore we cannot draw causal conclusions, and other unknown confounders may influence the result. It is of paramount importance to analyze covariance in a retrospective cohort study. We attempted to include a wide range of clinically important confounders to reach valid results and performed PSM to account for group differences.We used the multivariable logistic regression to adjust several clinically important confounders, like age, gender, ethnicity, temperature, mean blood pressure, SpO2, mechanical ventilation use, vasopressors use, comorbid heart disease, admission hemoglobin and so on. This association was maintained after adjusting to these clinically important confounders. APACHE IV scoring system had good discriminatory capability for critical patients[24, 25]. In the multivariable logistic regression analysis, we found that HcneHR was associated with NICU and hospital mortality after APACHE IV score was adjusted, indicating that HcneHR may provide prognostic information independent of APACHE IV score. The increasing trend of OR as the heart rate and cneHR increased may suggested dose-response relationship.The finding can help with prognosis prediction and raise the question about a causal relationship.

Our findings posed the question as to whether therapeutic reduction of HR is beneficial to neurocritical patients. For patients in septic shock, β-blocker was associated with reductions in heart rates to achieve target levels, without increased adverse events, and with a lower twenty-eight day mortality[26]. A meta-analysis of nine observational studies showed in adults with acute TBI, exposure to β-blockers after TBI was associated with a reduction of in-hospital mortality (pooled OR 0.39, 95%CI: 0.27–0.56; I2=65%, p<0.00001)[27]. There is a growing body of evidence showing that perioperative β-blocker exposure was associated with lower rates of 30-day all-cause mortality in cardiac high-risk patients undergoing noncardiac surgery[28]. Nevertheless, the right timeframe for intervention and the appropriate heart rate

goals are currently undefined. Further studies are required to investigate strategies for HR control in NICU patients. Appropriately randomized controlled multi center trials are required to confirm these questions.

The neurocritical care unit is a dataintensive environment. Utilization of these dense data onto realtime decisionmaking for patient care represents the art of neurocritical care practice[7]. Despite advances in medicine, data onto vital signs of bedside monitors in neurocritical care are evaluated by clinicians almost in much the same way as before. In one study of NICU patients, the investigator rather than just displayed the maximum daily temperature as the measure of fever, calculated the area under the curve (AUC) above a specific cutoff (such as >38.5 °C) and provided a morerobust measure of 'dose' of fever[29]. In Olaf Sander's study prolonged elevated HR (PEHR) group was defined as >95 beats/min for >12 hours in at least one 24-hour period of ICU stay starting at admission[5]. And in Veit Sandfort's study a prolonged eHR (peHR) episode was prespecified as 11 hourly heart rate measurements >100 beats/min in any given 12-hour interval [16]. These are examples of 'dose' parameters. In other studies, measures of HR volatility (standard deviation, % HR >120 bpm, and %HR<60 bpm) were used to predict prognosis[30, 31]. In our study, cneHR was used as an index to evaluate HR, it was also a 'dose' and 'volatility' parameter. It can reflex duration of elevated HR, on the flip side may present HR volatility. Most importantly, cneHR can be displayed in real time at the bedside because it can be acquired and calculated automatically.

In general, the large sample size, inclusion of multiple NICUs, and the excellent quality of the clinical data collection by the treatment centers, for example, the periodic heart rate is available for 96% of patients, are advantages of this analysis. The chosen variable to define 'dose' and 'volatility'of elevated HR was found to be suitable to identify patients with an increased risk of mortality in the NICU. However, there are several limitations of our study. Firstly, the study is retrospective, its post hoc nature should be taken into account when considering the findings. Residual confounding may also influence our findings, although we attempted to account for this through several adjustments and different models. Secondly, although the datasets we used are large and comprise routinely collected clinical data, some patients had to be excluded owing to poor-quality data recording or missing data. The amount of missing data onto the hemoglobin assessed in the study is a potential limitation. In the stepwise regression analysis, hemoglobin was contained in the final model. Because of the missing data, we dropped it in the predictive model. Thirdly, in eICU-CRD, all patients admitted from the operating room or recovery room had a surgical diagnosis, even though some surgical patients have a medical reason for admission. That may to some extent change disease spectrum. Although our findings do support an association with HcneHR and NICU mortality, stronger evidence is necessary to establish a causal relationship.

Conclusions

In adult neurocritically ill patients , HcneHR in the first day of NICU stay is independently associated with higher NICU mortality and several others important patient-centered outcomes.

Abbreviations

NICU：Neurological intensive care unit

HcneHR: high cumulative numbers of elevated Heart Rate

eICU-CRD: eICU Collaborative Research Database

APACHE: Acute Physiology and Chronic Health Evaluation

IRB: institutional review board SpO2: pulse oxygen saturation

NOCB: observation carried backward ROC: receiver operating characteristic

TBI: traumatic brain injury AUC: area under curve

Declarations

Acknowledgments

We thank the anonymous reviewers for insightful and helpful comments.

Funding: This study was supported by grants from key support projects of “Yangfan Plan” of Beijing Medical Administration(NO.ZYLX201836).

Availability of data and materials

The datasets generated and analysed during the current study are available in the eICU Collaborative Research Database(eicu-crd.mit.edu).

Authors’ contributions

DWZ, JXZ and GZS were responsible for the concept and participated the design of the study. DWZ, ZML and SLZ participated the data collection and the data analysis and interpretation. DWZ, JXZ and GZS participated the statistical analysis. DWZ and GZS wrote the first draft of the manuscript. All authors commented on the manuscript revisions and approved the final version.

Ethics approval and consent to participate

The eICU-CRD was exempt from institutional review board approval due to the retrospective design, lack of direct patient intervention, and the security schema, for which the re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA) (Health Insurance Portability and Accountability Act Certification no. 1031219-2). Due to the HIPAA compliant de-identification in this database, our institutional IRB requirement was waived. Patient’s consents were waived due to the retrospective design of the study.

Consent for publication: Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Strobe Statement

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page-1	Title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page-3 and Page-4	Abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page-4	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Page-5	Introduction
Methods				
Study design	4	Present key elements of study design early in the paper	Page-5, 6, 7, 8 and Page-9	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page-5	Methods: Setting
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page-6	Methods: Study Population
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Not applicable	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and	Page-6 and Page-7	Methods

		effect modifiers. Give diagnostic criteria, if applicable		
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page-7	Methods
Bias	9	Describe any efforts to address potential sources of bias	Page-15 and Page-16	Discussion
Study size	10	Explain how the study size was arrived at	Page-6	Methods
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page-7	Statistical Analysis
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page-7,8 and Page-9	Statistical Analysis
		(*b*) Describe any methods used to examine subgroups and interactions	Page-8 and Page-9	Statistical Analysis
		(*c*) Explain how missing data were addressed	Page-8	Statistical Analysis
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Not applicable	
		(*e*) Describe any sensitivity analyses	N/a	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure-1	
		(b) Give reasons for non-participation at each stage	Figure-1	
		(c) Consider use of a flow diagram	Figure-1	

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page-9	Results
		(b) Indicate number of participants with missing data for each variable of interest	Page-10	Results
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/a	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time *Case-control study*—Report numbers in each exposure category, or summary measures of exposure Page-9 and Page-10 Results *Cross-sectional study*—Report numbers of outcome events or summary measures Table-1		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page-10, Table-2	Results
		(*b*) Report category boundaries when continuous variables were categorized	Page-7	Methods
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/a	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page-11, Figure-3	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	Page-11 and Page-12	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page-15 and Page-16	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page-12, 13, 14, 15 and Page-16	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page-15 and Page-16	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page-16	Funding

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Tables

Table 1 Comparison of baseline characteristics between alive and expired patients

Variables	Total(n=8347)	Alive(n=8008)	Expired(n=339)	P value
Age,years (meadian,[IQR])	63(51,75)	63(51,75)	67(54,77)	0.002
Sex:male(n(%))	4312(52)	4118(51)	194(57)	0.041
Admission vital sign				
Temperature,C(meanSD)	36.47±0.82	36.47±0.79	36.37±1.42	0.18
Respiratory rate(meanSD)	23.21±14.45	23.1±14.43	25.98±14.49	<0.001
HR,beats/min(meanSD)	97.05±30.45	96.4±30.22	112.3±31.88	<0.001
MBP,mmHg(meanSD)	99.17±42.67	99.31±42.45	96.01±47.61	0.211
SpO2,%(meadian,[IQR])	98(96,100)	98(96,100)	99(96,100)	<0.001
Heart Rate related indexes for continuously monitoring				
cneHR (meadian,[IQR])	35.81±67.07	34.26±65.39	72.5±91.58	<0.001
HcneHR (n(%))	3082(37)	2874(36)	208(61)	<0.001
MaxHR,beats/min(meanSD)	105.17±20.25	104.65±19.91	117.48±23.96	<0.001
MinHR,beats/min(meanSD)	65.19±14.94	65.01±14.83	69.56±16.88	<0.001
AHR,beats/min(meanSD)	80.92±15.11	80.57±14.93	89.23±16.92	<0.001
APS (meanSD)	38.59±20.96	37.26±19.42	70.09±29.6	<0.001
APACHE IV score(meanSD)	49.61±22.82	48.21±21.44	82.53±28.87	<0.001
Hemoglobin,g/dl(meanSD)	11.79±2.02	11.8±2	11.57±2.38	0.077
Ethnicity(n(%))				0.355
Caucasian	6298(75)	6053(76)	245(72)	
African American	1128(14)	1077(13)	51(15)	
Hispanic	287(3)	278(3)	9(3)	
Asian	128(2)	122(2)	6(2)	
ative American	59(1)	57(1)	2(1)	
Other/Unknown	447(5)	421(5)	26(8)	
Disease category(n(%))				<0.001
Postoperation	2111(25)	2060(26)	51(15)	
Ischemic stroke	1576(19)	1516(19)	60(18)	

Traumatic brain injury	1197(14)	1150(14)	47(14)	
Intracranial hemorrhage	799(10)	731(9)	68(20)	
Seizures	373(4)	365(5)	8(2)	
Sepsis	283(3)	255(3)	28(8)	
Subarachnoid hemorrhage	233(3)	218(3)	15(4)	
Coma	179(2)	161(2)	18(5)	
Others	1596(19)	1552(19)	44(13)	
Atrial fibrillation(n(%))	229(3)	214(3)	15(4)	0.078
Cardiovascular Diseases(n(%))	2395(29)	2269(28)	126(37)	0.001
Tracheal intubation(n(%))	1290(15)	1123(14)	167(49)	<0.001
Mechanical ventilation(n(%))	1880(23)	1655(21)	225(66)	<0.001
Vasopressors(n(%))	371(4)	304(4)	67(20)	<0.001
NICU LOS(days) (meanSD)	4.17±4.75	4.12±4.72	5.26±5.34	<0.001

IQR interquatile range, SD standard deviation,HR heart rate,HcneHR high cumulative numbers of elevated Heart Rate,MaxHR maximum heart rate, MinHR minimum heart rate, AHR average heart rate,SpO2 Pulse Oxygen Saturation,APS Acute physiology score, APACHE Acute Physiology and Chronic Health Evaluation, NICU neurologic intensive care unit, LOS length of stay

Table 2 Crude primary and other outcomes between HcneHR and LcneHR patients

Variables	Total(n=8347)	LcneHR(n=5265)	HcneHR(n=3082)	P value
NICU Expired(n(%))	339(4)	131(2)	208(7)	<0.001
Hospital Expired(n(%))	669(8)	295(6)	374(12)	<0.001
NICU LOS(days) (meanSD)	4.17±4.75	3.83±4.3	4.76±5.39	<0.001
APS(meanSD)	38.59±20.96	34.08±18.06	46.29±23.2	<0.001
APACHE IV score(meanSD)	49.61±22.82	45.58±20.5	56.48±24.86	<0.001
Tracheal intubation(n(%))	1290(15)	605(11)	685(22)	<0.001
Mechanical ventilation(n(%))	1880(23)	943(18)	937(30)	<0.001
Vasopressors(n(%))	371(4)	164(3)	207(7)	<0.001

HcneHR high cumulative numbers of elevated Heart Rate, LcneHR low cumulative numbers of elevated Heart Rate, NICU neurologic intensive care unit, LOS length of stay, APS Acute physiology score, APACHE

Acute Physiology and Chronic Health Evaluation.

Table 3 Unadjusted and adjusted odds ratio for NICU and hospital mortality by cneHR

Model	HcneHR for NICU mortality		HcneHR for hospital mortality	
	OR (95% CI)	P value	OR (95% CI)	P value
Unadjusted	2.84 (2.27-3.55)	<0.001	2.33(1.98-2.73)	<0.001
Model 1	1.62 (1.27-2.06)	<0.001	1.42(1.19-1.69)	<0.001
Model 2	1.59 (1.27-2.04)	<0.001	1.51(1.27-1.81)	<0.001
Model 3	1.50 (1.09-2.08)	0.014	1.37(1.09-1.74)	0.008
Final model	1.57 (1.23-2.00)	<0.001	1.50(1.24-1.79)	<0.001
Predictive model	1.57 (1.23-2.01)	<0.001	1.39(1.16-1.65)	<0.001

model 1 adjusted for APACHE IV score; model 2 adjusted for demographics, age, gender, ethnicity and APACHE IV score; model 3 adjusted for model 2 covariates plus disease categories, admission vital sign(temperature, respiratory rate, heart rate, mean blood pressure,Spo2), the first day hemoglobin, use of mechanical ventilation, use of vasopressors, length of NICU stay, comorbidities, including atrial fibrillation, cardiovascular diseases. Stepwise backward elimination with a significance level of 0.05 was used to build the final model. Predictive model used APACHE IV score, use of mechanical ventilation, use of vasopressors and HcneHR as covariates.

NICU neurologic intensive care unit, OR odds ratio, cneHR cumulative numbers of elevated Heart Rate, HcneHR high cumulative numbers of elevated Heart Rate.

Supplemental File Figure Legends

Supplementary fig. 1 : Left: cneHR between alive and expired patients in NICU; Right: cneHR between alive and expired patients in hospital

Supplementary fig. 2: ROC analysis of cneHR for NICU mortality

Supplementary fig. 3: Odds Ratio of different disease subgroups for hospital expired patients

Supplementary fig. 4: ROC analysis of predictive model

Figures

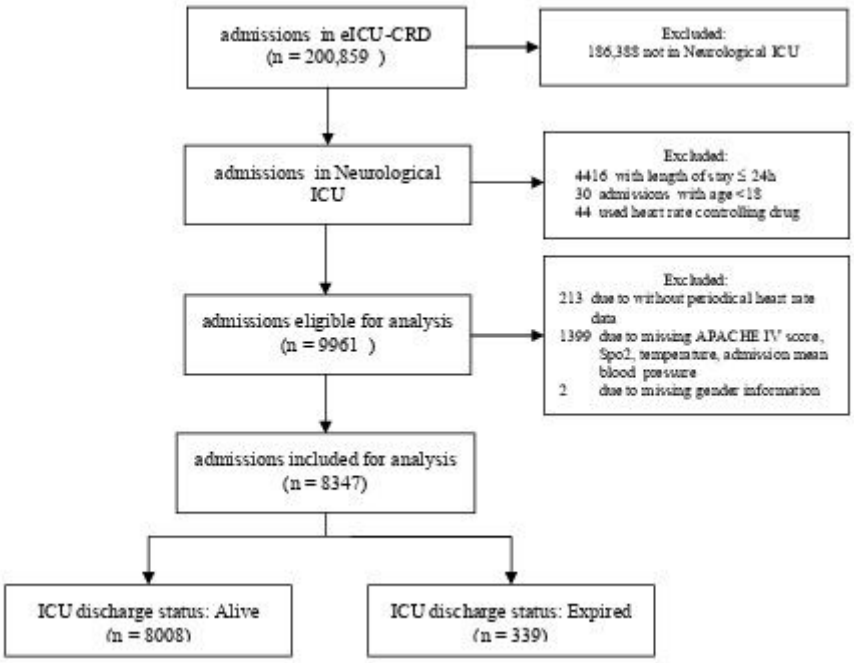

Figure 1

Flow chart of subject selection

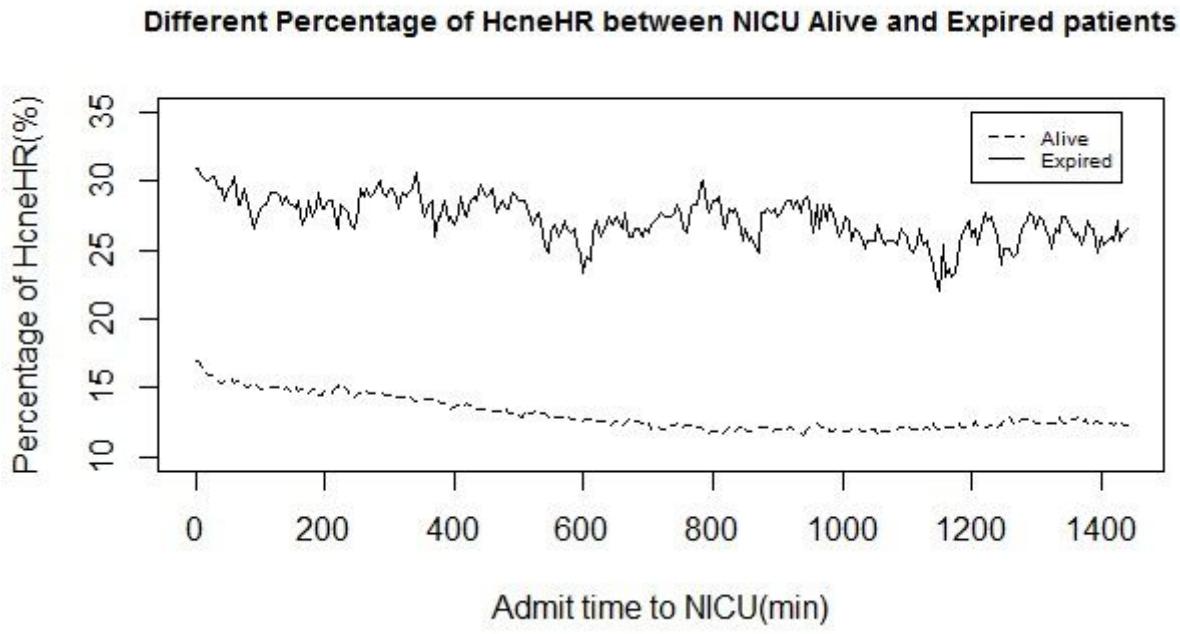

Figure 2

different percentage of HcneHR between NICU alive and expired patients over time

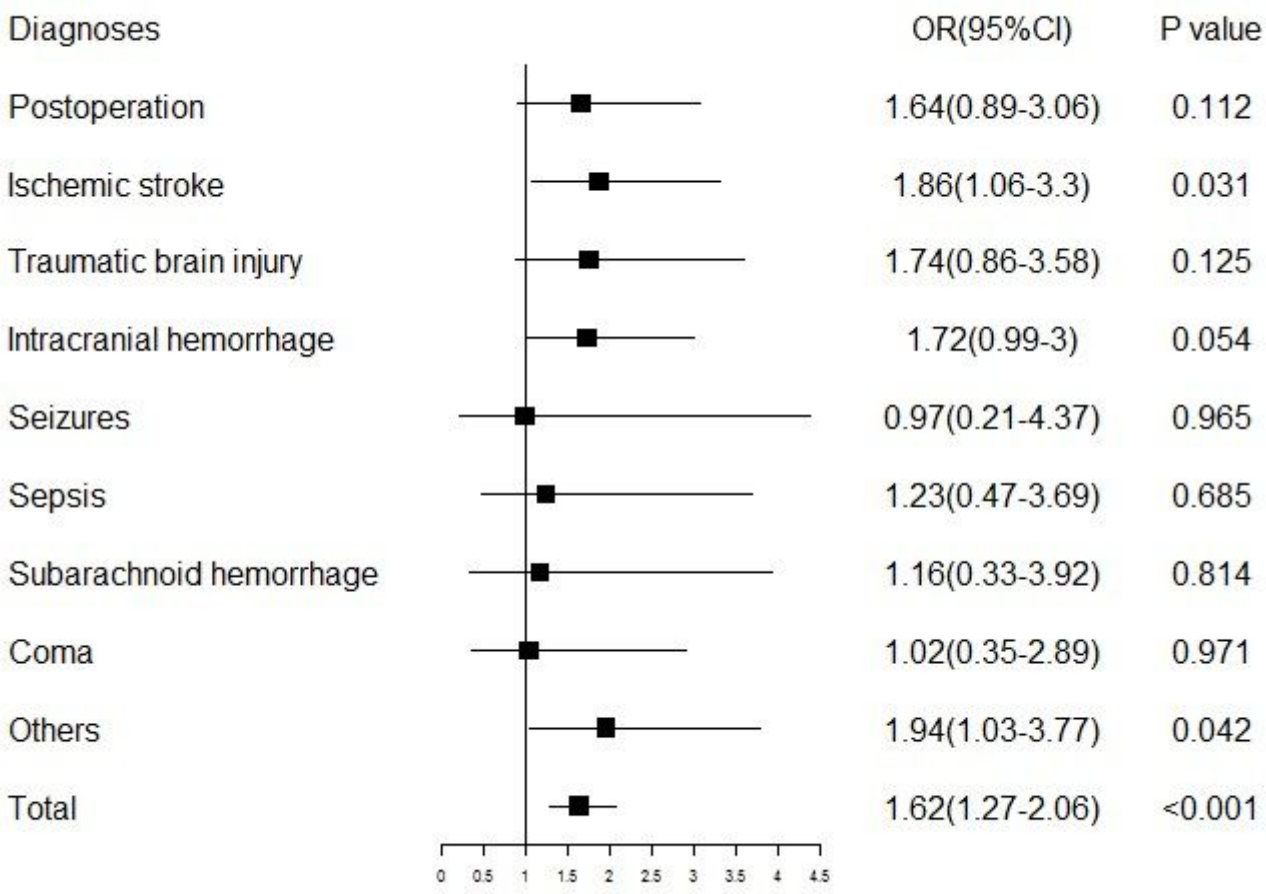

Figure 3

Odds Ratio of different disease subgroups for NICU expired patients

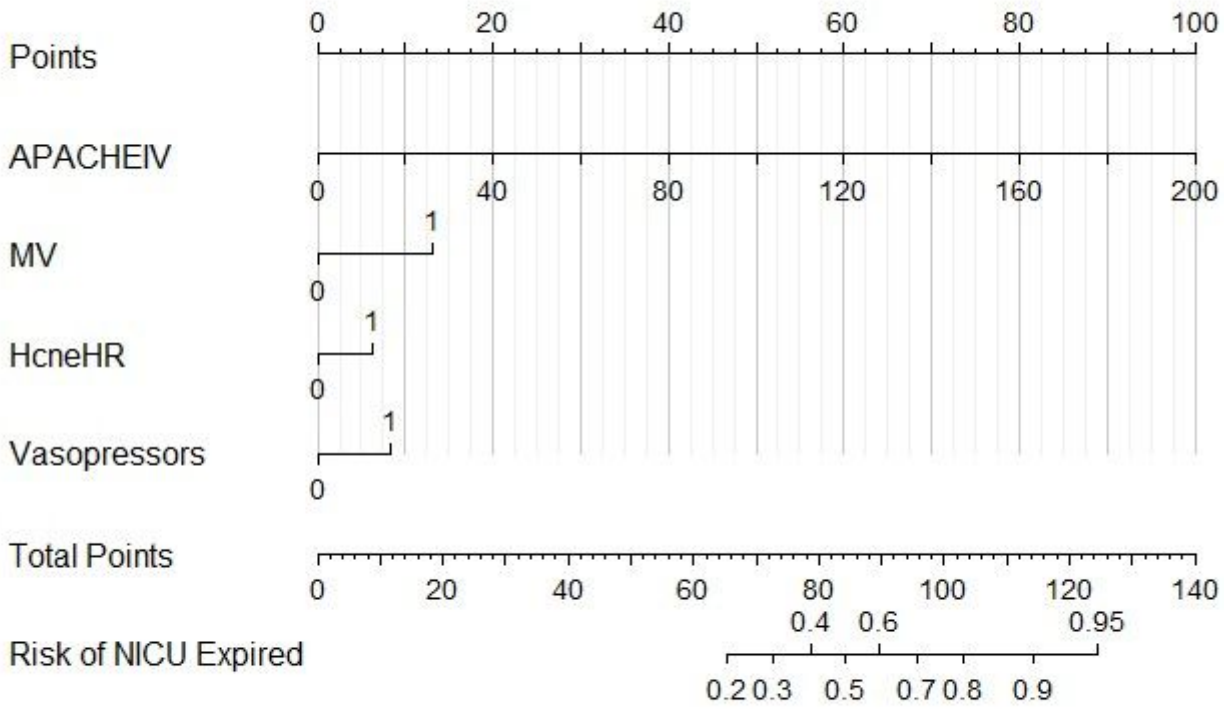

Figure 4

Nomogram of predictive model for the risk of death for NICU patients

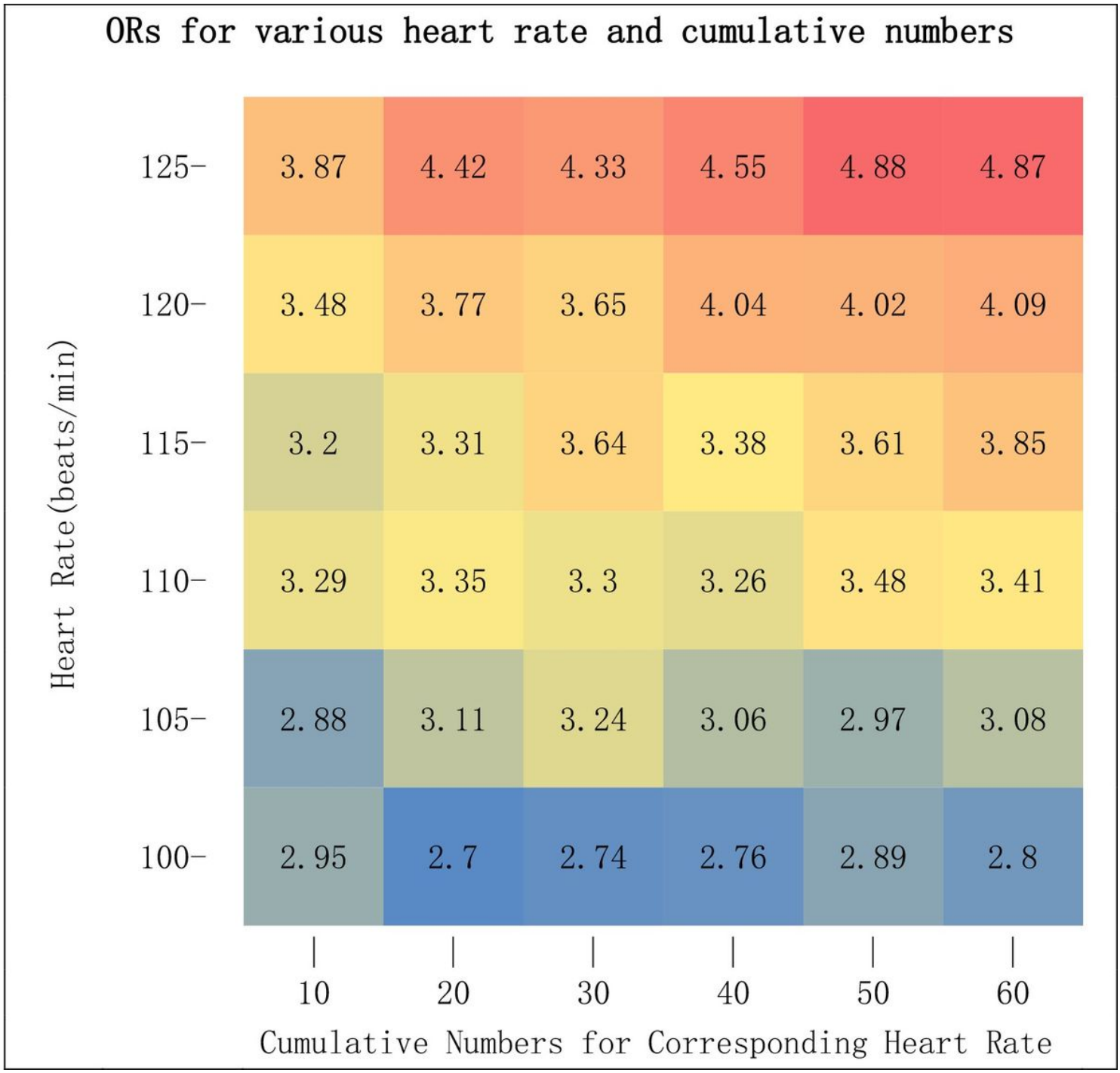

Figure 5

odds ratio for various heart rate and cumulative numbers over corresponding heart rate

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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- Supplementaryfig.4.tiff

- Supplementaryfig.3.tiff
- Supplementaryfig.2.tiff