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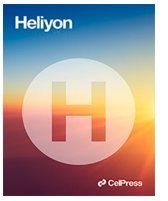

Research article

Heart/breathing rate ratio (HBR) as a predictor of mortality in critically ill patients

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ABSTRACT

Objectives: The early prediction of death is a challenge for medical staff. We evaluated the ability of the heart/breathing rate ratio (HBR) to predict mortality.
Methods: This was a single-center retrospective observational study of adult patients who had fever with or without respiratory symptoms, who survived at least 2 h after visiting the hospital, and whose lactate levels and vital signs were tested. We evaluated the distribution of mortality at different HBR levels and compared HBR with lactate.
Results: A total of 18,872 fever clinic visits were screened, and 183 patients whose lactate levels were tested were recruited. Patients who had HBR values lower than 4·5 or higher than 5·5 had greater mortality than patients who had HBR values between 4·5 and 5·5 (21·3 % vs. 3·4 %, $p = 0·003$; 28·9 % vs. 3·4 %, $p < 0·001$, respectively). In patients whose HBR was <5, the AUROC for HBR for mortality was 0·762 (95 % CI: 0.643–0·880), and that for lactate was 0·701 (95 % CI: 0·564–0·837). In patients whose HBR was ≥5, the AUROC for HBR for mortality was 0·721 (95 % CI: 0·584–0·857), and that for lactate was 0·742 (95 % CI: 0·607–0·848).
Conclusions: HBR is helpful for stratifying mortality risk among critically ill patients in acute care clinics for infectious diseases.

1. Introduction

The fever clinic is an acute care clinic that is open for 24 h and is usually a part of the infectious diseases department, where patients with fever symptoms are treated. These patients included outpatients, emergency patients, and critically ill patients. Our clinic visits more than 17,000 people annually, some of whom are critically ill. Failure to recognize and respond to deteriorating adult patients in a timely manner has been identified as an international patient safety concern [1–7]. Although the National Early Warning Score

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(NEWS), quick Sequential Organ Failure Assessment (qSOFA), lactate level and other indices are available for evaluating the level of risk, quick recognition of poor prognosis is still a challenge for various medical staff. There is an urgent need for a tool that can quickly and favorably determine the prognosis of patients with fever in the clinic without the aid of any instruments.

The NEWS can be used to effectively identify high-risk patients [8–10], but the ambulance medical staff does not routinely provide this information in our center-based region, and much work is needed to complete the chart despite the patient's status. Lactate level detection is also believed to be useful in critically ill patients but is not always available in minutes for all centers due to the different hospital settings, and frequent arterial blood collection and costs are not always accepted by patients. Studies have shown that qSOFA is more specific but less sensitive; therefore, international guidelines for the management of sepsis and septic shock 2021 recommend against using qSOFA as a single screening tool for sepsis or septic shock [11–14].

Traditionally, in China, doctors do not have clocks, thermometers or sphygmomanometers; they have no conditions for calculating scores such as the NEWS, but there are still numerous medical books recorded on how to predict death. One of them is the pulse/breathing rate ratio (PBR). At least 1000 years ago, ancient traditional Chinese medicine physicians have determined that a PBR that is not 4–5 predicts "death". Most modern doctors believe that PBR disorder refers to immediate death within minutes; therefore, there are few studies on PBR as a predictor of mortality. In practice, some PBR "disordered" patients do not die on the spot but may die in the near future or experience very poor clinical outcomes.

The associations of lactate levels with mortality in patients with suspected infection and sepsis are well established [15–17]. A majority of the SEPSIS-3 task force agreed that an elevated lactate level is reflective of cellular dysfunction in sepsis [18].

The initial PBR with no treatment can be a predictor of mortality, and our center recorded heart rate; thus, we evaluated the ability of the heart/breathing rate ratio (HBR) to predict mortality.

2. Results

We evaluated 18,772 fever clinic visits and identified 200 patients who were tested for lactate levels between May 2020 and June 2021. After exclusions, as noted in Fig. 1, 183 patients were included in the analysis. The median (Q1, Q3) age of the patients was 75 (65,84) years. There were 36 (20 %) patients who died within 30 days, 15 (8 %) who were admitted to the ICU, and 3 (1·6 %) who discontinued treatment with mechanical ventilation therapy. The mean heart rate was 106 per minute in the whole study population, 110 in the nonsurvivor group, and 105 in the survivor group. The mean breathing rate was 23 per minute in the whole study population, 25 in the nonsurvivor group, and 23 in the survivor group. The HBR was 4·76 in the whole study population, 4·8 in the nonsurvivor group, and 4·75 in the survivor group. The patients' baseline characteristics are presented in Table 1.

Mortality, ICU admission and discontinuation of treatment with mechanical ventilation therapy during HBR are presented in Fig. 2 (A-C). The HBR had the lowest effect on any of the outcomes, with scores between 4 and 5. Patients who had HBR values lower than 4·5

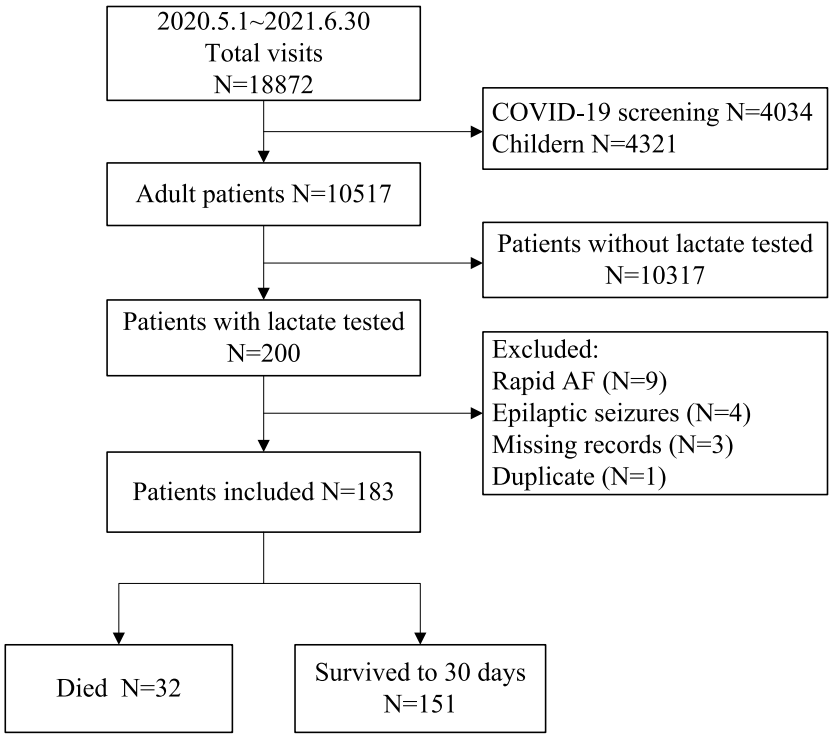

Fig. 1. Flow chart of screened and included patients. Note: AF: Arterial fibrillation.

Table 1
Baseline characteristics. This table seems splitted into two parts, and I have no idea how to fix this.

Variable	Overall, N = 183[a]	Prognosis		p-value[b]
		Survivors	Non survivors	
		N = 151 (83 %)[a]	N = 32 (17 %)[a]	
Age	75.00 [65.00, 84.00]	76.00 [65.00, 84.00]	72.00 [67.75, 81.00]	0.598
Heart rate	102.00 [90.00, 120.50]	100.00 [89.00, 116.50]	118.50 [100.00, 127.75]	0.012
Breathing rate	21.00 [20.00, 25.00]	21.00 [19.50, 25.00]	23.00 [20.00, 29.25]	0.114
HBR	4.75 [3.92, 5.39]	4.77 [4.02, 5.29]	4.27 [3.29, 6.00]	0.657
BP	135.00 [114.50, 155.50]	139.00 [120.00, 156.00]	117.00 [94.50, 137.25]	0.002
SpO2	96.00 [91.50, 97.00]	96.00 [92.50, 98.00]	93.00 [88.00, 95.25]	<0.001
Temp	38.21 (1.00)	38.21 (1.01)	38.22 (0.97)	0.946
NEWS	7.00 [4.00, 10.00]	7.00 [4.00, 9.00]	11.00 [7.00, 13.00]	<0.001
0–4, n (%)	48 (26.23 %)	48 (31.79 %)	0 (0.00 %)	
5–6, n (%)	30 (16.39 %)	25 (16.56 %)	5 (15.63 %)	
7–8, n (%)	38 (20.77 %)	34 (22.52 %)	4 (12.5 %)	
9–10, n (%)	25 (13.66 %)	19 (12.58 %)	6 (18.75 %)	
11–12, n (%)	22 (12.02 %)	16 (10.60 %)	6 (18.75 %)	
13–14, n (%)	15 (8.20 %)	7 (4.64 %)	8 (25.00 %)	
≥15, n (%)	5 (2.73 %)	2 (1.32 %)	3 (9.38 %)	
Lactate	1.80 [1.20, 2.90]	1.70 [1.10, 2.58]	2.95 [1.78, 4.30]	<0.001
< 2, n (%)	103 (56.28 %)	92 (60.93 %)	11 (34.38 %)	
2–5, n (%)	67 (36.61 %)	53 (35.10 %)	14 (43.75 %)	
≥5, n (%)	13 (7.10 %)	6 (3.97 %)	7 (21.88 %)	
Sex				0.333
Female	74 (40.44 %)	64 (42.38 %)	10 (31.25 %)	
Male	109 (59.56 %)	87 (57.62 %)	22 (68.75 %)	
Consciousness				0.002
Unconscious	58 (31.69 %)	40 (26.49 %)	18 (56.25 %)	
Conscious	125 (68.31 %)	111 (73.51 %)	14 (43.75 %)	

Variable	Overall, N = 183[a]	Prognosis		p-value[b]
		Survivors	Non survivors	
		N = 151 (83 %)[a]	N = 32 (17 %)[a]	
Primary diagnosis				
Infectious disease				0.059
No	12 (6.56 %)	7 (4.64 %)	5 (15.63 %)	
Yes	171 (93.44 %)	144 (95.36 %)	27 (84.38 %)	
Pneumonia				0.775
No	45 (24.59 %)	36 (23.84 %)	9 (28.13 %)	
Yes	138 (75.41 %)	115 (76.16 %)	23 (71.88 %)	
UTI				0.609
No	153 (83.61 %)	125 (82.78 %)	28 (87.50 %)	
Yes	30 (16.39 %)	26 (17.22 %)	4 (12.50 %)	
Cholecystitis				0.129
No	170 (92.90 %)	138 (91.39 %)	32 (100.00 %)	
Yes	13 (7.10 %)	13 (8.61 %)	0 (0.00 %)	
Skin Infection				0.608
No	176 (96.17 %)	144 (95.36 %)	32 (100.00 %)	
Yes	7 (3.83 %)	7 (4.64 %)	0 (0.00 %)	
URTI				0.589
No	178 (97.27 %)	146 (96.69 %)	32 (100.00 %)	
Yes	5 (2.73 %)	5 (3.31 %)	0 (0.00 %)	
Other				>0.999
No	171 (93.44 %)	141 (93.38 %)	30 (93.75 %)	
Yes	12 (6.56 %)	10 (6.62 %)	2 (6.25 %)	
COMORBIDITIES				
Low potassium				0.206
No	165 (90.16 %)	134 (88.74 %)	31 (96.88 %)	
Yes	18 (9.84 %)	17 (11.26 %)	1 (3.13 %)	
High permeability				0.440
No	180 (98.36 %)	149 (98.68 %)	31 (96.88 %)	
Yes	3 (1.64 %)	2 (1.32 %)	1 (3.13 %)	
Electrolyte disturbance				0.457
No	148 (80.87 %)	120 (79.47 %)	28 (87.50 %)	
Yes	35 (19.13 %)	31 (20.53 %)	4 (12.50 %)	
Acidosis				0.075
No	173 (94.54 %)	145 (96.03 %)	28 (87.50 %)	
Yes	10 (5.46 %)	6 (3.97 %)	4 (12.50 %)	

(*continued on next page*)

Table 1 (*continued*)

Variable	Overall, N = 183[a]	Prognosis		p-value[b]
		Survivors	Non survivors	
		N = 151 (83 %)[a]	N = 32 (17 %)[a]	
Anemia				0.535
No	163 (89.07 %)	133 (88.08 %)	30 (93.75 %)	
Yes	20 (10.93 %)	18 (11.92 %)	2 (6.25 %)	
Thrombocytopenia				0.354
No	176 (96.17 %)	146 (96.69 %)	30 (93.75 %)	
Yes	7 (3.83 %)	5 (3.31 %)	2 (6.25 %)	
Acute heart failure				0.643
No	151 (82.51 %)	126 (83.44 %)	25 (78.13 %)	
Yes	32 (17.49 %)	25 (16.56 %)	7 (21.88 %)	
Acute kidney injury				0.505
No	166 (90.71 %)	138 (91.39 %)	28 (87.50 %)	
Yes	17 (9.29 %)	13 (8.61 %)	4 (12.50 %)	
Respiratory failure				0.001
No	149 (81.42 %)	130 (86.09 %)	19 (59.38 %)	
Yes	34 (18.58 %)	21 (13.91 %)	13 (40.63 %)	
Arrhythmia				0.273
No	169 (92.35 %)	141 (93.38 %)	28 (87.50 %)	
Yes	14 (7.65 %)	10 (6.62 %)	4 (12.50 %)	
Gastrointestinal hemorrhage				0.194
No	174 (95.08 %)	145 (96.03 %)	29 (90.63 %)	
Yes	9 (4.92 %)	6 (3.97 %)	3 (9.38 %)	
Shock				<0.001
No	144 (78.69 %)	127 (84.11 %)	17 (53.13 %)	
Yes	39 (21.31 %)	24 (15.89 %)	15 (46.88 %)	
Past history				
Diabetes				0.300
No	126 (68.85 %)	101 (66.89 %)	25 (78.13 %)	
Yes	57 (31.15 %)	50 (33.11 %)	7 (21.88 %)	
Cardiovascular disease				>0.999
No	110 (60.11 %)	91 (60.26 %)	19 (59.38 %)	
Yes	73 (39.89 %)	60 (39.74 %)	13 (40.63 %)	
Cerebrovascular disease				0.369
No	128 (69.95 %)	103 (68.21 %)	25 (78.13 %)	
Yes	55 (30.05 %)	48 (31.79 %)	7 (21.88 %)	
Nephropathy				0.744
No	155 (84.70 %)	129 (85.43 %)	26 (81.25 %)	
Yes	28 (15.30 %)	22 (14.57 %)	6 (18.75 %)	
Hepatopathy				0.790
No	155 (84.70 %)	127 (84.11 %)	28 (87.50 %)	
Yes	28 (15.30 %)	24 (15.89 %)	4 (12.50 %)	
Pulmonary disease				0.877
No	41 (22.40 %)	33 (21.85 %)	8 (25.00 %)	
Yes	142 (77.60 %)	118 (78.15 %)	24 (75.00 %)	
COPD				>0.999
No	168 (91.80 %)	138 (91.39 %6)	30 (93.75 %)	
Yes	15 (8.20 %)	13 (8.61 %)	2 (6.25 %)	
Pressure ulcers				>0.999
No	179 (97.81 %)	147 (97.35 %)	32 (100.00 %)	
Yes	4 (2.19 %)	4 (2.65 %)	0 (0.00 %)	
Tumor				0.046
No	166 (90.71 %)	134 (88.74 %)	32 (100.00 %)	
Yes	17 (9.29 %)	17 (11.26 %)	0 (0.00 %)	
Hypertension				0.007
No	113 (61.75 %)	86 (56.95 %)	27 (84.38 %)	
Yes	70 (38.25 %)	65 (43.05 %)	5 (15.63 %)	
Immunological diseases				0.354
No	176 (96.17 %)	146 (96.69 %)	30 (93.75 %)	
Yes	7 (3.83 %)	5 (3.31 %)	2 (6.25 %)	
Location of Death				
ED			17	
ICU			2	
Floor			9	
Other			4	
Time from Visit to Death				
Died within 24 h, n (%)			13 (40.61 %)	
Died within 3 days, n (%)			7 (21.88 %)	
Died within 7 days, n (%)			5 (15.63 %)	
Died within 30 days, n (%)			7 (21.88 %)	

Note: URTI: Upper respiratory tract infection; COPD: Chronic obstructive pulmonary disease; SpO2: Saturation of peripheral oxygen; HBR: Heart/Breathing rate ratio; SBP: Systolic Blood Pressure; ED: Emergency Department; ICU: Intensive Care Department.

[a] Median [IQR]; Mean (SD); n (%).

[b] Wilcoxon rank sum test; Welch Two Sample *t*-test; Pearson's Chi-squared test; Fisher 's exact test.

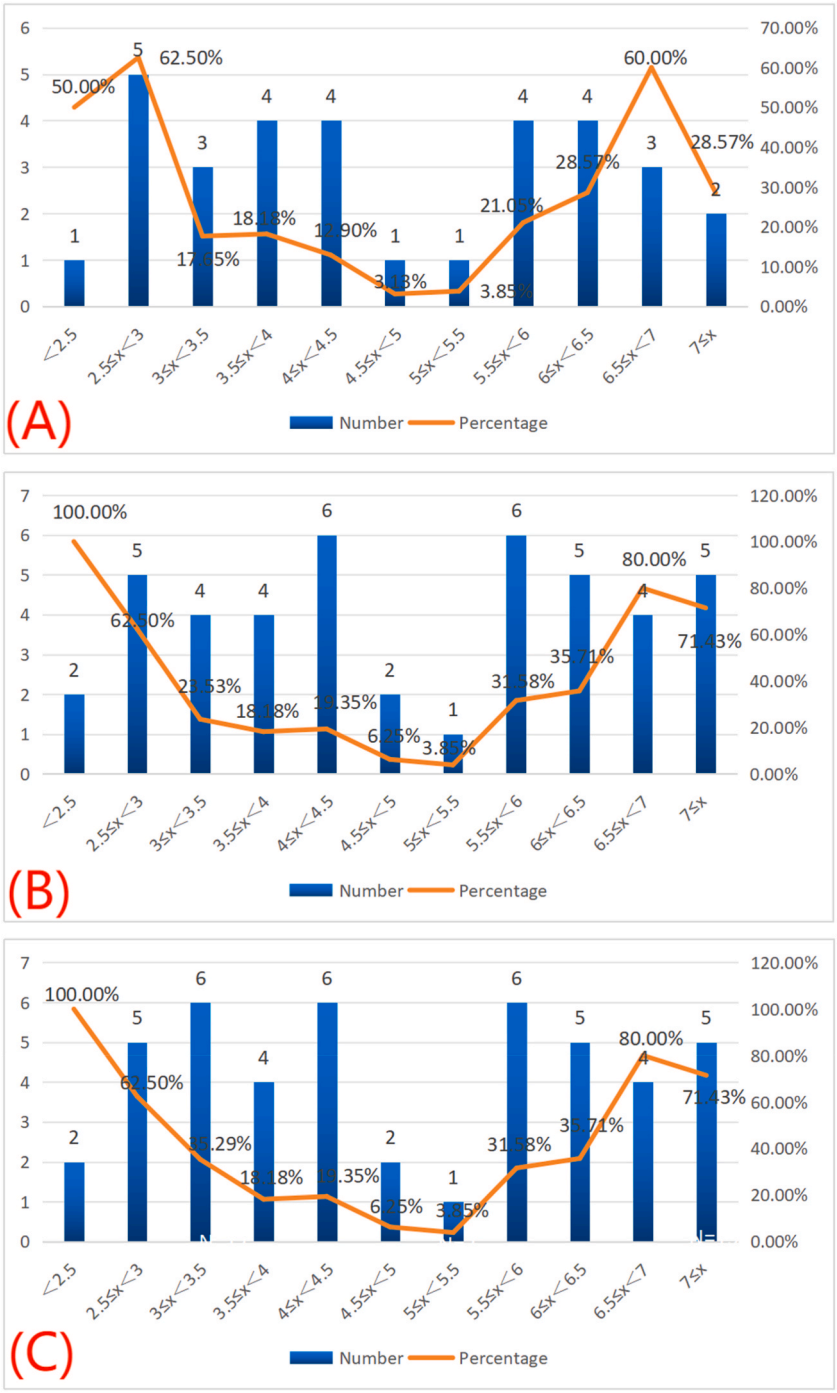

Fig. 2. Clinical outcomes by different HBR level. (A) Mortality by HBR. (B) Mortality and ICU admission by HBR. (C) Mortality, ICU admission and give up therapy during mechanical ventilation on the process by HBR.

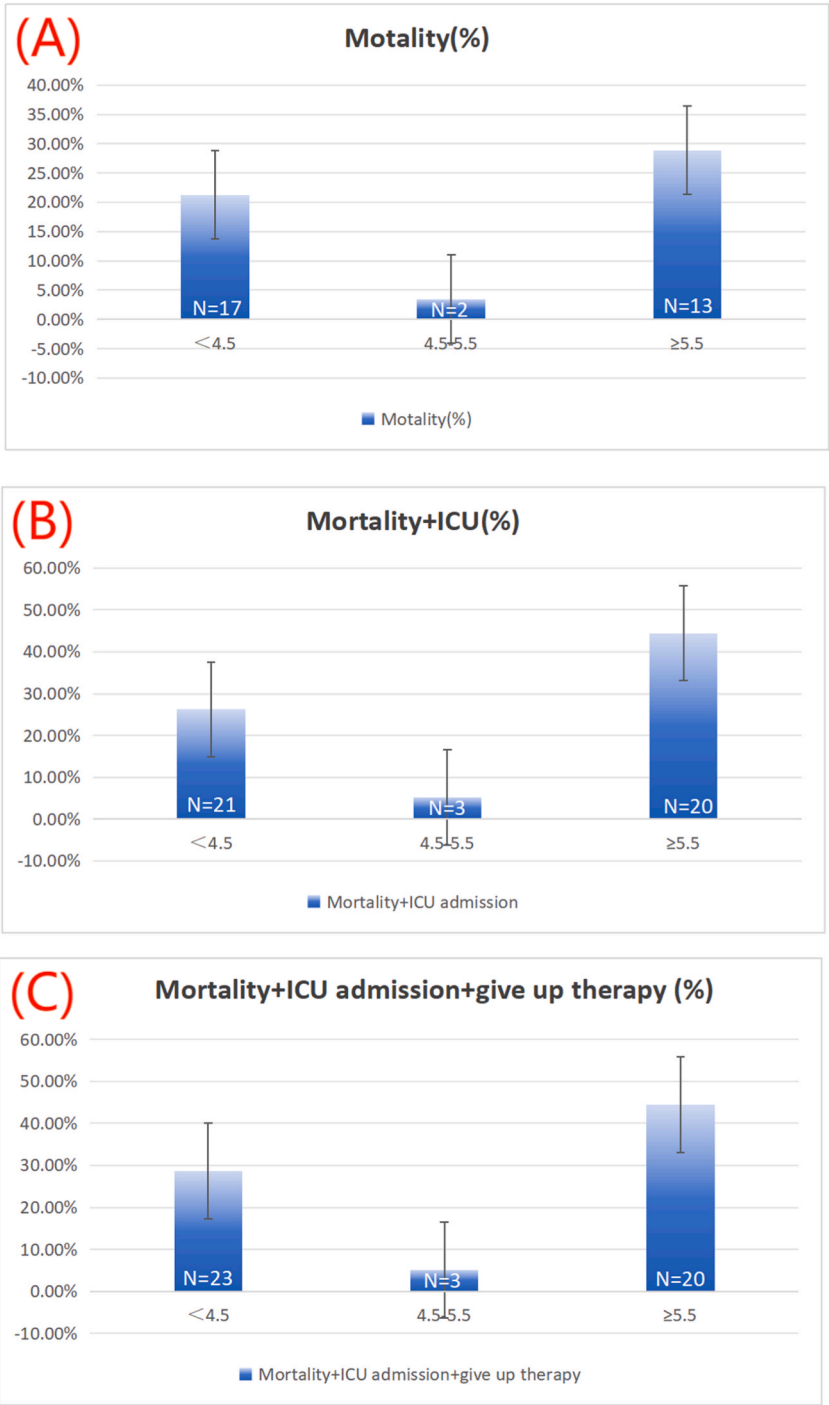

Fig. 3. Outcomes among "normal" and "disordered" HBR. (A) Mortality among "normal" and "disordered" HBR. (B) Mortality and ICU admission among "normal" and "disordered" HBR. (C) Mortality, ICU admission and give up therapy during mechanical ventilation on the process among "normal" and "disordered" HBR.

or higher than 5·5 had greater mortality than patients who had HBR values between 4·5 and 5·5 (21·3 % vs. 3·4 %, p = 0·003; 28·9 % vs. 3·4 %, p < 0·001, respectively). [Fig. 3 (A-C)].

2.1. Subgroup analysis

In patients with HBR<5, both HBR and lactate were strongly associated with mortality (AUC, 0·762 [95 % CI: 0·643–0·880] and 0·701 [95 % CI: 0·564–0·837], respectively). (Fig. 4A and B). In patients with HBR≥5, HBR and lactate both had reasonable associations with mortality (AUC 0·721 [95 % CI: 0·584–0·857] and 0·742 [95 % CI: 0·607–0·848], respectively). (Fig. 4C and D).

3. Discussion

As recorded in ancient Chinese medical books, one breath (one inhale and one exhale)with four to five pulses is normal, three or fewer pulses, or six or more pulses can predict "death". Considering the possibility of cutoff values existing between integers, we set an HBR interval of 0·5. Mortality increased when HBR was <4·5 or ≥5·5, and the incidence of death, intensive care unit (ICU) admission, and discontinuation of treatment with mechanical ventilation increased.

We defined patients who had lactate levels tested as critically ill patients for whom doctors' evaluations were the gold standard. Our center has ABGs with and without lactate, and only the patients whom the doctors believed to be critically ill or suspected of having sepsis had lactate tested. Our study population's baseline characteristics were consistent with those of other studies aimed at

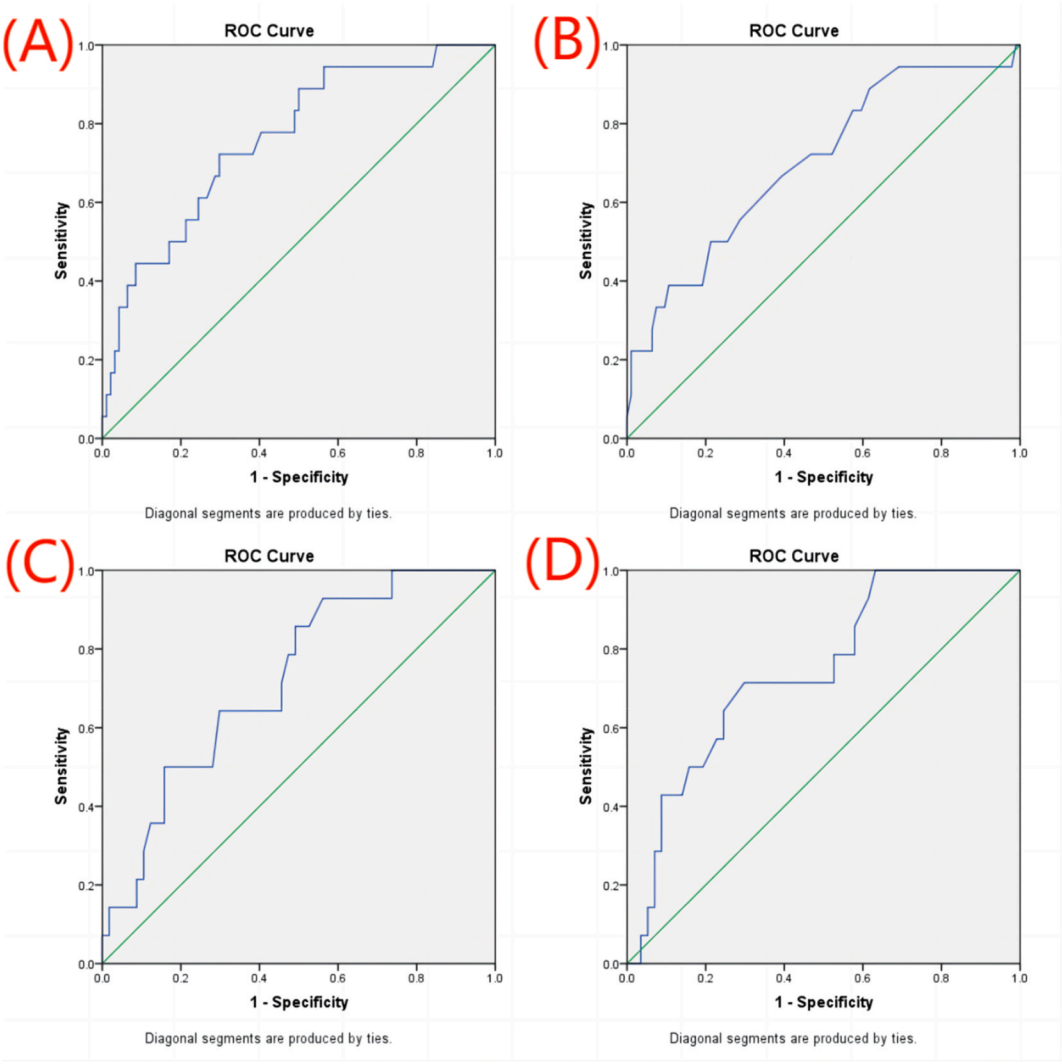

Fig. 4. The receiver operating curves of raw HBR or lactate for predicting death. (A) HBR by mortality in HBR < 5 patients. (B) Lactate by mortality in HBR < 5 patients. (C) HBR by mortality in HBR ≥ 5 patients. (D) Lactate by mortality in HBR ≥ 5 patients.

critically ill patients [19,20], and patients whose lactate levels were tested according to our center's practice were selected as the right population. In this particular population, HBR "abnormality" showed an incredibly high correlation with mortality.

Fig. 2 shows that the greater the HBR deviates from the "normal range" (4·5-5·5), the greater the combination incidence rate. Ancient Chinese doctors relied on PBRs to determine whether a patient was going to die. With the popularization of various medical equipment, the value of PBRs has been underestimated, and very few traditional Chinese medicine doctors still use PBRs in practice. Even in China, the authors can find no studies on this issue. To the best of our knowledge, this is the first study to use HBR as a predictor of mortality. Observing the relationship between breathing and pulse requires at least 30 s without the help of any tools. In the case of limited medical conditions, HBR can be a useful predictor of mortality in critically ill patients.

Elevated respiration is a powerful sign of acute illness and distress in all patients and is associated with elevated mortality risk in various settings. Evidence suggests that adults with a breathing rate greater than 20 breaths/min are likely unwell, those with a breathing rate greater than 22/min are likely to have elevated mortality, and those with a breathing rate greater than 24/minute are likely to be critically ill [21–26]. Thus, by measuring breathing rate these conditions can be detected [27]. A reduced breathing rate is indicator of central nerve system and narcosis. The body attempts to correct hypoxaemia and hypercarbia by increasing both tidal volume and breathing rate.

Heart rate is also an important indicator of showing patients' clinical condition, can reflect disease severity in patients with various medical conditions. While heart rate represents a compilation of physiological inputs, including sympathetic and parasympathetic tone [28]. Elevated heart rate is associated with mortality elevation [29–32], and there was an overall increase in mortality associated with increased heart rate which is clinically significant, with doubling of risk for every 40-bpm increase in heart rate [33].

Both breathing and heart rate are important, but the relationship between the two are not well studied. It is very uncommon for a significant disturbance of a single physiological parameter to occur in isolation. Thus, NEWS Development and Implementation Group believed multiple physiological parameters is a more robust measure of acute-illness severity than single-parameter scoring systems [34–38]. HBR as a combination index of two very important vital signs, the ratio may show the status of ventilation-perfusion to some degree. Unlike scoring systems as NEWS or qSOFA calculate scores such as vital signs, HBR imbalance reflects the disturbed oxygen/blood usage in the tissue. Lower HBR means reduced heart rate compared with breathing rate, the transmission of oxygen might be insufficient; higher HBR means reduced breathing rate compared with heart rate, the blood oxygen content was lowered. As we mentioned before, HBR was underestimated and not fully studied, but might reflecting tissue hypoxia and metabolic disorder. The relationship of HBR with NEWS also should be further studied.

There is a well-known association between lactate and mortality in critically ill patients [21]. In our study, both the HBR and lactate level were strongly associated with mortality, and the HBR had similar or even better predictive value for mortality than the lactate.

HBR measurement can be integrated into current clinical practices as the first step for critically ill patients in field or acute care settings by calculating one or two breaths along with pulses. Any deviation from a normal HBR could indicate an elevated mortality risk.

This study still has many unresolved problems. 1 During clinical practice, we also observed that after active treatment, the HBR of some patients returned to within the normal range, even those who died within hours. This means that only the raw HBR may have predictive value. 2 The main outcome incidence rate in this study was nearly 30 %, but the incidences in numbers were not high. In some groups, there were not enough incidences to analyze, especially in the HBR$<$2 or HBR$>$7 groups. 3 Our results were based on data extracted from the medical records system, and some of the HBR data may not reflect the initial status without any treatment. Our hypothesis is that some critically ill patients have already received at least oxygen therapy in the ambulances without being recorded in the system.

The strength of any conclusions for this study is that it was limited by the use of data collected retrospectively from a single center. The previous medication records were not complete for all aspects of what we needed; thus, we did not consider the effect of the intervention during the analysis. We were not able to confirm the status of the patients who discontinued therapy. The HBR showed a bowl-like distribution in predicting mortality; thus, we selected the midpoint of the "normal" range to separate the study population into two groups. All AUROC analyses were performed under this setting, which might have led to bias. Further multicenter prospective studies using larger and more robust registry datasets are needed to validate our results.

4. Conclusion

The HBR is helpful for stratifying mortality risk in critically ill patients in acute care settings for infectious diseases.

5. Materials and methods

5.1. Population

This was a retrospective single-center observational study at a fever clinic between May 2020 and June 2021. Patients were selected from the medical records system and laboratory test system. The data collected included patient demographics and clinical outcomes.

The HBR is defined as the heart/breath ratio, and this particular department's medical record system records heart rate but not pulse; thus, we studied HBR as a predictor.

In this study, we recognized critically ill patients as those who had their lactate levels tested since the doctors prescribed lactate testing to those who were considered septic or who were simply "critically ill" in fever clinics.

Inclusion criteria: All patients who visited a fever clinic, aged $\geq$16 years, and had a lactate level tested along with a full vital sign

record prior to treatment (within 30 min of this visit).

Exclusion criteria: Patients with prehospital treatment were excluded in order to observe the outcome of the initial HBR. Patients who died within 2 h were excluded; there was no need for HBR to predict mortality since those patients were dying at that time. Patients with rapid atrial fibrillation and epilepsy at the time of admission were also excluded because of their negative effects on HBR and lactate levels, respectively.

As a routine part of clinical care, fever clinic nurses record vital signs each time they were measured. The following data were recorded at the bedside or triage: date/time of observation set; heart rate; systolic blood pressure; breathing rate; body temperature; neurological status using the Alert-Verbal-Painful-Unresponsive (AVPU) scale; and peripheral oxygen saturation (SpO2). The HBR was subsequently calculated, and the lactate level was extracted from the laboratory test result searching system.

The measured outcomes studied were death, intensive care unit (ICU) admission, and discontinuation of treatment with mechanical ventilation therapy. Traditionally, Chinese people believe that "leaves wither and fall on the ground by the tree roots"; if possible, relatives want patients to die in their own home. Many patients choose to return home when they realize that they have no chance to survive. Therefore, we considered discontinuation of treatment with mechanical ventilation as an outcome measure. All the outcomes were identified from the medical records. We analyzed the presence of any of these outcomes within 30 days.

Diagnoses were obtained through medical record review. For patients with more than one diagnosis, the primary diagnosis was selected by the first author after consensus with the patient's doctor in charge.

5.2. Statistical analysis

All data manipulation was performed using Microsoft® EXCEL 2020. Baseline characteristics are presented with descriptive statistics. Continuous variables are presented as the means and standard deviations or medians and interquartile ranges (IQRs) or 25 % quantiles or 75 % quantiles (Q1, Q3), as appropriate, depending on the normality of the data. Differences between groups were tested using Student's *t*-test or Wilcoxon's rank-sum test. Categorical data are presented as counts and proportions, with differences between groups tested using the chi-square test or Fisher's exact test.

Associations between HBR and mortality, ICU admission, and discontinuation of treatment with mechanical ventilation therapy were analyzed by proportion description. Lactate was evaluated as a categorical variable both for simplicity and based on prior literature suggesting that the categorical approach was as predictive as using lactate as a continuous variable [39]. Subgroup analysis of HBR and lactate levels was performed using the area under the receiver operating characteristic (AUROC) curve. AUROC analysis is performed using SPSS v22. The minimum AUROC possible is 0·5, which is the value that would be expected if the model was no better than chance at predicting mortality. Reasonable discrimination is indicated by AUROC values of 0·7 to 0·8, and good discrimination is indicated by values exceeding 0·8.

Ethics approval statement

The authors ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals and aims for the inclusion of representative human populations (sex, age and ethnicity) as per those recommendations. This study was approved by the Ethics Committee of the SAHTUTCM (2021-013-01), and informed consent was waived by the ethics committee. The privacy rights of human subjects were observed.

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Data sharing

The data associated with our study have not been deposited into a publicly available repository due to reasons of privacy and sensitivity. However, deidentified individual participant data will be made available from authors upon reasonable request to zhangtongyan610@126.com. Proposals for use of the data will be reviewed and approved by the SAHTUTCM steering committee.

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CRediT authorship contribution statement

Tong Yan Zhang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Ya Jun Du:** Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Ya Zhu Hou:** Methodology, Formal analysis, Data curation, Conceptualization. **Qian Du:** Methodology, Data curation, Conceptualization. **Hai Rong Dou:** Validation, Methodology, Data curation. **Xiu Mei Gao:** Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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