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(RESEARCH ARTICLE)

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The Kaplan-Meier survival analysis of the dual sodium related comparative Jordanian critically ill cohorts whose major administered antibiotics were beta-lactams

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Abstract

Background: Abnormal serum sodium levels in various diseases increase mortality; however, hyperglycemia depresses serum sodium concentration significantly.

Aim: This study aimed to evaluate the clinical impact of measured serum sodium levels and corrected sodium levels among Jordanian critically ill cohorts whose major administered antibiotics were Beta-Lactams

Methods: This study was retrospectively conducted in the Intensive Care Unit (ICU) to primarily investigated the 2 proposed Na-based prognosticators against the overall mortality for the admitted critically ill patients in the Intensive Care Unit (ICU) at the King Hussein Medical Center between Jan 2018 and May 2021, after approval by the Royal Medical Services, Jordan local Institutional Review Board committee (IRB). A Kaplan-Meier test was conducted on the tested critically ill patients to explore the "time-to-event" during their admission days in the ICU and to determine if there were differences in the survival distribution for the different types of the 2 investigated dual different Na-related comparative cohorts [Measured Na related Events Cohort vs Measured Na related Censored Cohort and Corrected Na related Event Cohort vs Corrected Na related Censored Cohort]. Also, the Survival Kaplan-Meier test was used to plot the Survival functions' illustrations for each tested Na-related mortality prognosticator.

Results: The survival distributions for the 2 investigated dual comparative cohorts were statistically significantly different [$\chi 2$ (3) = 30.454, p-value=0.000 and $\chi 2$ (2) = 23.411, p-value=0.000, respectively] at Mean±SEM overall LOS of [21.444±0.138 days (95% CI; 21.173-21.714) and 21.444±0.138 days (95% CI; 21.173-21.714), respectively] and Number (%) of both Event and Censored cohorts of [1715 (79.6%) vs 440 (20.4%), respectively].

Conclusion: Our study revealed that both the measured and corrected hyponatremia had significant prognostic performances regarding major clinical outcomes when critically ill patients were studied regardless of their blood levels.

Keywords: Measured sodium; Corrected sodium; Hyperglycemia; Mortality; Critical illness; Kaplan-Meier Survival analysis

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1. Introduction

Dysnatremia circumstances or dysnatremias in the admitted hospitalized critically or even non-critically ill patients may manifest as independent prognostic surrogates' major clinical impacts, including particularly length of stay days (LOS) and mortality rates. Dysnatremias, which is simply identified as a variation of the sodium level from the normal limit, pose a common finding in admitted critically ill patients on either on admission or during their stay. It is expectedly for hospitalized admitted patients, upon admission or during the stay, to present with or acquire dysnatremias [1-4].

Hyponatremia, defined biochemically as a sodium level lower than 135 mEq/L, is frequently associated with critically ill patients, especially with those who have accompanied heart, liver, lung, brain, and renal disturbances. As with hypernatremia, hyponatremia is an indicator of disease severity and poor prognosis. Additionally, hyponatremia is associated with increased mortality while urgent Na concentration over-correction owing to the higher propensity of central pontine myelinolysis state (osmotic demyelination syndrome of the pons) leading to quadriparesis [5-7].

In this study, we aimed to conduct Kaplan-Meier Survival Analysis for the tested patients' overall survival rate during their length of stay in the critical care unit at the King Hussein Medical Center, Royal Medical Services, Jordan between Jan 2018 and May 2021.These Jordanian critically ill cohorts were administered Beta-Lactams antibiotics as major antibiotics.

2. Material and methods

This study was retrospectively conducted in the Intensive Care Unit (ICU) to primarily investigated the 2 proposed Na-based prognosticators against the overall mortality for the admitted critically ill patients in the Intensive Care Unit (ICU) at the King Hussein Medical Center between Jan 2018 and May 2021, after approval by the Royal Medical Services, Jordan local Institutional Review Board committee (IRB). In this study, we studied all admitted critically ill patients, including mechanically or non-mechanically ventilated critically ill patients whose studied variables were accessible from our institutional Electronic Medical Record System (Hakeem). Patients who had primarily missed data on the primarily investigated parameters or the comparatively tested variables will be excluded from our study.

A Kaplan-Meier test was conducted on the tested critically ill patients to explore the "time-to-event" during their admission days in the ICU and to determine if there were differences in the survival distribution for the different types of the 2 investigated dual different Na-related comparative cohorts [Measured Na related Events Cohort vs Measured Na related Censored Cohort and Corrected Na related Event Cohort vs Corrected Na related Censored Cohort]. Also, the Survival Kaplan-Meier test was used to plot the Survival functions' illustrations for each tested Na-related mortality prognosticator. The event was determined in this study as "All-cause mortality" and the time was identified as "Length of ICU stay". The pre-determined upper-time limit in this study was sat for maximally 2 months. Any admitted critically ill patient who survived the 2-months or was discharged before, was allocated to the censored cohort. Analysis results were expressed as Numbers (Percentages) for the event and censored cohorts. The LOS was also presented as Mean±SEM (95% CI; Lower-Upper). The survival distributions of the different investigated sodium variables were primarily tested via the Log Rank (Mantel-Cox) test which calculates a χ2-statistic (the "Chi-Square" column), that compares a χ2-distribution with two degrees of freedom (df). Also, we adjunctively used the Breslow (Generalized Wilcoxon) and Tarone-Ware tests to test the null hypothesis of no differences in the overall survival distributions across the investigated cohorts.

Analyses were performed using SPSS for Windows, version 25 (SPSS Inc., Chicago, IL, USA). Statistical significance was considered as $p < 0.05$.

3. Results

The survival distributions for the 2 investigated dual comparative cohorts were statistically significantly different [χ^2 (3) = 30.454, p-value=0.000 and χ^2 (2) = 23.411, p-value=0.000, respectively] at Mean±SEM overall LOS of [21.444±0.138 days (95% CI; 21.173-21.714) and 21.444±0.138 days (95% CI; 21.173-21.714), respectively] and Number (%) of both Event and Censored cohorts of [1715 (79.6%) vs 440 (20.4%), respectively].

The total cases for the tested Na related group were 8, 1147, 994, and 6 for the Na ranges of <120, 120-<129, 130-<139, and 140-<149, respectively, with an overall of 1715. The corresponding events percentages were 100%,.5%, 69%, and 100%, respectively. Regarding the corresponding censored rates, they were stated as 0 (0%), 132 (11.5%), 308 (31%), and 0 (0%), respectively, with an overall of 440 (20.4%). The Means±SEMs were also investigated at 19.375±1.972

(95% CI; 15.509-23.241), 21.224±0.155(95% CI; 20.920-21.529), 21.881±0.237 (95% CI; 21.417-22.345), and 19.000±3.033 (95% CI; 13.055-24.945), respectively, with an overall of 21.444±0.138 (95% CI; 21.173-21.714).

While the total cases for the corrected sodium prognosticator were 643, 1503, and 9 for the cNa ranges of 120-<129, 130-<139, and 140-<149, respectively. The corresponding censored events' percentages were evaluated at 509 (91.8%), 1116 (74.3%), and 9 (100%), respectively. Alternatively, the censored rates were stated as 53 (8.2%), 387 (25.7%), and 0 (0.0%), respectively, with an overall rate of 440 (20.4%). The cNa Means±SEMs were investigated at 20.953±0.196 (95% CI; 20.568-21.338), 21.737±0.182 (95% CI; 21.381-22.093), and 19.000±2.369 (95% CI; 14.357-23.643), respectively, with an overall Means±SEMs of 21.444±0.138 (95% CI; 21.173-21.714).

The Kaplan-Meier test analysis results and the survival functions' illustrations for the tested patients' overall survival rate during their length of sta. y in the critical care unit at the King Hussein Medical Center were presented in **Table 1** and **Figure 1**, respectively.

Table 1 The Kaplan-Meier test analysis results for the tested patients' overall survival rate during their length of stay in the critical care unit at the King Hussein Medical Center, Royal Medical Services, Jordan between Jan 2018 and May 2021

	Total N	**Events N (%)**	**Censored N (%)**	**Mean±SEM**	**95% CI**		**Log Rank (Mantel-Cox) Breslow (Generalized Wilcoxon) Tarone-Ware**
					Lower	**Upper**	
Na (mEq/l)							
<120	8	8 (100.0%)	0 (0.0%)	19.375±1.972	15.509	23.241	χ^2 (3) = 30.454, p-value=0.000 χ^2 (3) = 4.989, p-value=0.173 χ^2 (3) = 16.823, p-value=0.001
120-129	1147	1015 (88.5%)	132 (11.5%)	21.224±0.155	20.920	21.529	
130-139	994	686 (69.0%)	308 (31.0%)	21.881±0.237	21.417	22.345	
140-149	6	6 (100.0%)	0 (0.0%)	19.000±3.033	13.055	24.945	
Overall	2155	1715 (79.6%)	440 (20.4%)	21.444±0.138	21.173	21.714	
cNa (mEq/l)							
120-129	643	590 (91.8%)	53 (8.2%)	20.953±0.196	20.568	21.338	χ^2 (2) = 23.411, p-value=0.000 χ^2 (2) = 6.807, p-value=0.033 χ^2 (2) = 14.534, p-value=0.001
130-139	1503	1116 (74.3%)	387 (25.7%)	21.737±0.182	21.381	22.093	
140-149	9	9 (100.0%)	0 (0.0%)	19.000±2.369	14.357	23.643	
Overall	2155	1715 (79.6%)	440 (20.4%)	21.444±0.138	21.173	21.714	
The Kaplan-Meier test was conducted on the tested critically ill patients to explore the "time-to-event" during their admission days in the ICU. The event was determined in this study as "All-cause mortality" and the time was identified as "Length of ICU stay". The pre-determined upper-time limit in this study was sat for maximally 2 months. Any admitted critically ill patient who survived the 2-months or was discharged before, was allocated to the censored cohort. Analysis results were expressed as Numbers (Percentages) for the event and censored cohorts. The LOS was also presented as Mean±SEM (95% CI; Lower-Upper). The survival distributions of the different investigated sodium variables were primarily tested via the Log Rank (Mantel-Cox) test which calculates a χ2-statistic (the "Chi-Square" column), that compares a χ2-distribution with two degrees of freedom (df). Also, we adjunctively used the Breslow (Generalized Wilcoxon) and Tarone-Ware tests to test the null hypothesis of no differences in the overall survival distributions across the investigated cohorts.							
Na^+: The measured sodium level in mEq/l			**cNa^+:** The corrected sodium level in mEq/l.				

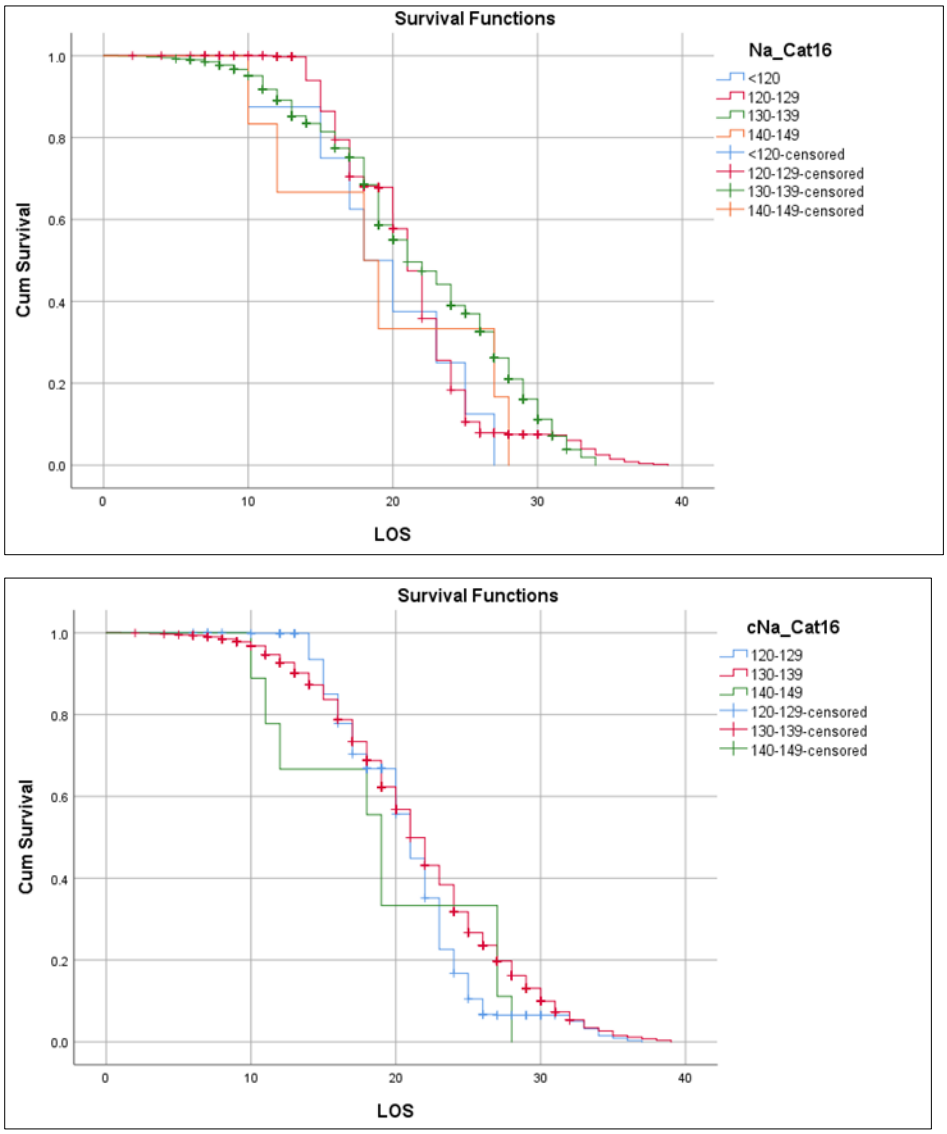

Figure 1 The Kaplan-Meier Survival functions' illustrations of the 2 investigated dual different Na-related comparative cohorts [Measured Na-related Events Cohort vs Measured Na-related Censored Cohort and Corrected Na-related Event Cohort vs Corrected Na related Censored Cohort] on admitted critically ill patients at the King Hussein Medical Center, Royal Medical Services, Jordan between Jan 2018 and May 2021

4. Discussion

This study primarily demonstrated the clinical impact of 2 investigated Na-based mortality-related prognosticators, Measured Na Levels, and Corrected Na Levels, in admitted critically ill patients. The uniqueness of this study was involved in its conducted methods. We first conducted a Survival Kaplan-Meier analysis to show the significance of survival distribution during the ICU admission days.

In our study, the mean LOS±SEM for 1147 tested patients [1015 died (88.5%) vs132 censored (11.5%)] whose measured Na levels ranged from 120 mEq/l to 129.9 mEq/l was 21.224±0.155 days (95% CI; 20.920-21.529) compared to 20.953±0.196 days (95% CI; 20.568-21.338) in 643 tested patients [590 died (91.8%) vs 53 censored (8.2%)] who had corrected Na levels in the same range.

Despite their statistical significance in this study, the measured and corrected Na levels' prognostic utilities, unadjusted HRs [(1.330 (95 CI; 1.207- 1.466), $\chi 2$ (1) = 33.259, <0.001) vs (1.354 (95% CI; 1.229-1.491), $\chi 2$ (1) = 37.792,

<0.001), respectively], and even though the adjusted HRs were clinically insignificant. Contrarily to the aforementioned previous studies which included mostly severe hyperglycemic patients, this retrospective observational study compared both the measured and corrected Na concentrations of all admitted eligible critically ill patients regardless of their blood levels. Additionally, several previous studies concluded that patients with hyponatremia-related congestive heart failure (CHF), chronic kidney diseases (CKD), hemorrhagic or ischaemic stroke, and liver-cirrhosis were independently associated with statistically and clinically substantial poor prognosis, including higher mortality rates and admission days. In these aforementioned co-morbidities, it has been theorized that the hyponatremia statuses are primarily secondary to sympathetic, vasopressin, and renin hypersecretion storms [8-11].

5. Conclusion

Compared to the debated conclusions of previous studies regarding the prognostic superiority of corrected over-measured Na concentrations, our study revealed that both the measured and corrected hyponatremia had significant prognostic performances regarding major clinical outcomes, especially overall mortality and admission days.

Compliance with ethical standards

Acknowledgement

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript.

Statement of ethical approval

There is no animal/human subject involvement in this manuscript.

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

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