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Piperacillin/tazobactam associated hypernatremia impacts on SARS-COV-2 infected patients

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Abstract

Objectives: The consequences of antibiotics-associated non-nutritional hypernatraemia may have a positive clinical impact on the mitigation of the COVID-19 related hyponatremia complications. This study aimed to explore the positive utility of Piperacillin/Tazobactam-associated sodium loading in COVID-19 patients.

Methods: A retrospective study was conducted between Mar 2020 and Sep 2021. Eligible patients were stratified into two antibiotics-based cohorts; Non-Tazocin Cohort and Tazocin Cohort. One-Sample and Independent T-Tests and Chi-Square Test were conducted and the corrected sodium and its changes from baseline were run into the Receiver Operating Characteristics Tests followed by Sensitivity analysis.

Results: The incidence of hyponatremia was significantly higher in Cohort I compared to Cohort II [378 (100.0%) vs 248 (61.5%), respectively, p-value=0.00]. The corrected sodium concentration was significantly lower in Cohort I compared to Cohort II [134.85±4.59 mEq/l vs 137.19±4.93 mEq/l, -2.34±0.34 mEq/l, p-value=0.00]. The mortality risk estimate for our institutional COVID-19 on PIP/TAZ vs Non-PIP/TAZ was 0.98 (95% CI; 0.74-1.29). 1.215 (95% CI; 0.85-1.73).

Conclusion: Piperacillin/Tazobactam antibiotics administration in SARS-CoV-2 infected patients may have a non-antibiotic mortality benefit via its clinically significant propensity to mitigate the risk of hyponatremia-related negative clinical consequences, including mortality. This study investigated that it was optimally to keep averaged sodium concentrations above 133.85 mEq/l and to restrict dropping in sodium concentration by more than 1.95% from baseline.

Keywords: Piperacillin/Tazobactam; β-lactam antibiotics; Carbapenems; Antibiotic-associated hypernatremia; Severe COVID-19 infected patients

1. Introduction

The coronavirus pandemic 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, represents the largest global public health crisis humanity has faced over time. Once declared as a pandemic in March 2020, COVID-19 affected more than 200 countries and infected more than 527,631,000 people, with 6,282,602 deaths as of May 25, 2022. This fatality rate varies according to countries, regions, and ethnicity and sex. Although the

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death rate has fluctuated alarmingly with each passing day, older adults with COVID-19 and those with comorbidities are at high risk of developing severe/critical conditions and being redirected to severe/critical [1-7].

Patients infected with SARS-CoV-2 can experience a series of complications differently. One of these recently identified COVID-19 related complications, which has been linked to worse clinical outcomes and mortality, is electrolyte dysfunction and, most importantly, hyponatremia. The most identifiable risk of induction of hyponatremia in hospitalized SARS-CoV-2-infected patients is all engraved in the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Indeed, the COVID-19 related hyponatraemia manifestations can be irregularly predicted and there is a good correlation between the amplitude of cytokine storms associated acute respiratory syndrome (ARDS) and hyponatremia grade [8-15].

In contrast, hypernatremia is occurred in critically ill patients with a prevalence of 7% ± 3% or 16% ± 10% for surgical and medical critical ill patients, respectively. These ICU related hypernatraemia cases are attributed to the administration of hypertonic solutions, irrigation and resuscitation crystalloids, , enteral and parenteral feeding, and Antibiotic-associated non-nutritional hypernatremia (AANNH). The AANNH is commonly manifested in hospitalized patients, with a prevalence of 0.2% upon admission and 1% during admission., and is a frequent concern in hospitalized patients who are taking β-lactam ABs, especially Piperacillin/Tazobactam [16-22].

Interestingly, the concerns of AANNH may balance the risk of COVID-19-associated hyponatremia. In our study, we aim to explore if the Piperacillin/Tazobactam-related sodium loading may have a clinical positive effect when compared with other Non-Piperacillin/Tazobactam antibiotics.

2. Material and methods

A single-center, non-sponsored and funded retrospective study was conducted over 19 months, between Mar 2020 and Step 2021, in a specialized COVID-19 isolation center at Queen Alia Military Hospital of the Royal Medical Services (RMS) in Jordan. All suspected or confirmed, mild/moderate-severe/critical SARS-CoV-2 infected Jordanian patients were included in our study. This study was ethically approved by our Jordanian Royal Medical Services-Ethical Review Board (JRMS-IRB) [Ref# 22/02_2022]. Approval was granted for us to only access data from the institutional Electronic Medical Record system (EMR, Hakeem) that were relevant to our study.

We retrospectively retrieved our tested admitted SARS-CoV-2 infected patients' data of social demography (age and gender), COVID-19 infection severity (according to World Health Organization for COVID-19 severity). Affected COVID-19 patients' survival considered points in our study were pre-defined as the point in which admitted SARS-CoV-2 infected patients were either survived 28-day or discharged before, which one comes first.

Infectious diseases prognosticator's ratios, including c-reactive protein (CRP) to albumin ratio (CRP: ALB), and ferritin to albumin ratio (FER: ALB) were also assessed. Sodium levels were corrected according to blood glucose. COVID-19 patient's severity, based on World Health Organization was stratified upon admission into mild/moderate grade (non-severe) when there was an absence of sign of severe or critical COVID-9 infections, severe grade when the SpO2 <90% on room air, respiratory rate >30 breath per minute, or critical grade when the severe COVID-19 infection was associated with ARDS, sepsis, or septic shock.

Eligible patients were stratified into two antibiotics-based cohorts; SARS-CoV-2 infected patients who were on any administered ABs except Piperacillin/Tazobactam (Non-PIP/TAZ Cohort, Cohort I) and affected COVID-19 patients who were administered Piperacillin/Tazobactam for at least 3 days during admission (PIP/TAZ Cohort, Cohort II). Firstly, the two cohorts were statistically analyzed using via One-Sample and Independent T-Tests to express as Means±SDs and Mean diff±SEM of each tested comparative variable across the two tested groups. Secondly, the dichotomous and categorical variables were crossed in SPSS to yield the incidences of occurrence as Number (Percentage), the Pearson chi-square statistic (χ 2), the likelihood-ratio chi-square statistic (G 2), and the odds ratio if statistically can be computed. Thirdly, we ran the participant's cNa_2 (1st tested prognosticator) and $\%\Delta Na_{12}$ (2nd tested prognosticator) into the Receiver Operating Characteristics (ROCs) Tests to investigate the area under the ROC curve (AUROC) of the tested prognosticator regarding its prognostic utility to for overall 28-day mortality. Fourthly, we expressed the optimal cut-off points, sensitivities, specificities, positive and negative predictive values, Youden and accuracy indices, and the negative likelihood ratios for cNa_2 and $\%\Delta Na_{12}$ for the overall COVID-19 infected patients' mortality through Sensitivity Analysis Test. Statistical analysis was performed using Statistical Package for Social Science (SPSS) software version 23.0. Statistical significance was set at 5%.

3. Results

Of the total admitted COVID-19 infected patients in our isolation departments at Queen Alia Military Hospital, Royal Medical Services, Amman, Jordan between Mar 2020 and Sep 2021, 718 eligible studied patients were finally included in this study (718/4183, 18.67%) in which 247 COVID-19 infected patients (31.6%) had suspected COVID-19 infection [117 (34.1%) belonged to **Cohort I** and 130 (29.7%) belonged to **Cohort II**] and 534 COVID-19 infected patients (68.4%) had confirmed COVID-19 infection [378 (48.39%) belonged to **Cohort I** and 403 (51.61%) belonged to **Cohort II**].

The mean age of the whole study cohort was 59.40±10.60 years, and **Cohort I** was insignificantly older than **Cohort II** (59.61±10.76 years versus 59.21±10.46 years, respectively, +0.40±0.76-year, P-value=0.599). Insignificantly, males were distributed in the study in approximately 2.309:1 ratio compared to females [545 (69.8%) versus 236 (30.2%), respectively, p-vale=0.556] in which 260 (68.8% COVID-19 infected men) and 118 (31.2% COVID-19 infected women) belonged to the **Cohort I** compared to 285 (70.7% COVID-19 infected men) and 118 (29.3% COVID-19 infected women) have belonged to the **Cohort II.**

Oxygen supply strategies for the whole studied cohort were insignificantly distributed between **Cohort I** and **Cohort II**, in which 90 (23.8%), 107 (28.3%), 98 (25.9%), and 83 (22.0%) versus 87 (21.6%), 116 (28.8%), 105 (26.1%), and 95 (23.6%) were on non-O_2 supply, nasal cannula at a flow rate of 3-6 L/min, non-invasive mechanical ventilation, and invasive mechanical ventilation, retrospectively, p-Value=0.881.

The insignificantly higher proportion of the eligible tested COVID-19 infected patients was on Dexamethasone 6 mg/day compared to None [405 (51.9%) vs 376 (48.1%)]. The proportional distribution of Dexamethasone 6 mg/day administration was insignificantly lower in **Cohort I** compared to **Cohort II** [197 (52.1%) vs 208 (51.6%), p-Value=0.888].

Average corrected sodium level (cNa_2) was significantly lower in Cohort I compared to Cohort II [134.85±4.59 mEq/l vs 137.19±4.93 mEq/l, -2.34±0.34 mEq/l, p-value=0.00] and the incidence of hyponatremia (cNa_2<140 mEq/l) was significantly higher in Cohort I compared to Cohort II [378 (100.0%) vs 248 (61.5%), respectively, p-value=0.00]. For investigated major clinical impacts, we showed that the overall hospital length of stay (LOS) and the 28-day overall SARS-CoV-2 infected mortality rate were significantly lower in Cohort I compared to Cohort II [11.57±1.591 days and 69 (18.3%) vs 11.64±1.595 days and 86 (21.3%), respectively, p-value=0531 and 0.280]. The mortality risk estimate for our institutional COVID-19 on PIP/TAZ vs Non-PIP/TAZ was 0.98 (95% CI; 0.74-1.29). 1.215 (95% CI; 0.85-1.73). Also, there were insignificant differences across the two tested cohorts among all remaining hematological and non-hematological investigated compared variables. All comparatively studied variables between Non-PIP/TAZ Cohort (Cohort I) and PIP/TAZ Cohort (Cohort II) among admitted COVID-19 infected patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021 were fully summarized in Tables 1-4. Also, the bar charts' visualizations for comparatively studied patient variables between Non-PIP/TAZ Cohort (Cohort I, Green Color) and PIP/TAZ Cohort (Cohort II, Blue Color) were illustrated in Figures 1-2.

Table 1 Comparatively studied variables between Non-PIP/TAZ Cohort (Cohort I) and PIP/TAZ Cohort (Cohort II) among admitted COVID-19 infected patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021

Studied Comparative Variables	**Overall Cohorts (N=781) Mean±SD**	**Cohort I (Non-PIP/TAZ Cohort) (N=378,48.39%) Mean±SD**	**Cohort II (PIP/TAZ Cohort)(N=403, 51.61%) Mean±SD**	**Mean Differences ±SEM**	**P-Value**
Age (Yrs)	59.40±10.60	59.61±10.76	59.21±10.46	0.40±0.76	0.599
BW (Kg)	73.73±10.02	73.34±9.74	74.09±10.28	-0.76±0.72	0.291
PARA dose (g/day)	1.90±0.94	1.89±0.93	1.92±0.95	-0.03±0.07	0.62
BG_1 (mg/dl)	283.1±78.0	281.5±78.8	284.6±77.4	-3.1±5.6	0.582
cNa_1 (mEq/l)	126.8±2.8	126.7±2.9	126.8±2.8	-0.1±0.2	0.782

BG $_2$ (mg/dl)	152.0±36.3	151.2±36.9	152.7±35.8	-1.5±2.6	0.576
cNa $_2$ (mEq/l)	136.06±4.91	134.85±4.59	137.19±4.93	-2.34±0.34	0.000
%Δ cNa$_{12}$	7.42%±5.42%	6.49%±5.18%	8.29%±5.51%	-1.80%±0.38%	0.000
HLOS	11.60±1.59	11.57±1.591	11.64±1.595	-0.072±0.114	0.531
Prescribed PIP/TAZ (mg/day)	11055±2574	0.0±0.0	11055±2574	NA	NA
Optimal** PIP/TAZ (mg/day)	12886±1547	0.0±0.0	12886±1547	NA	NA
Deficit*** PIP/TAZ (mg/day)	-3600±3248	0.0±0.0	-3600±3248	NA	NA
% Deficit PIP/TAZ	-25.0%±29.4%	0.0%±0.0%	-25.0%±29.4%	NA	NA
Prescribed MER (mg/day)	2092±648	2092±648	0.0±0.0	NA	NA
Optimal** MER (mg/day)	2532±500	2532±500	0.0±0.0	NA	NA
Deficit*** MER (mg/day)	-776±978	-776±978	0.0±0.0	NA	NA
% Deficit MER	-24.2%±39.8%	-24.2%±39.8%	0.0%±0.0%	NA	NA
Prescribed IMI/CIL (mg/day)	1215±348	1215±348	0.0±0.0	NA	NA
Optimal** IMI/CIL (mg/day)	1429±175	1429±175	0.0±0.0	NA	NA
Deficit*** IMI/CIL (mg/day)	-427±423	-427±423	0.0±0.0	NA	NA
% Deficit IMI/CIL	-27.4%±33.0%	-27.4%±33.0%	0.0%±0.0%	NA	NA

Data results of the comparative variables between the Group I and Group II were statistically analyzed by independent T and One-Sample T-Test (at p-value< 0.05) and expressed as Mean±SD and Mean difference±SEM.

Cohort I: COVID-19 infected patients who were on Non-PIP/TAZ (Imipenem or Meropenem).

Cohort II COVID-19 infected patients who were on PIP/TAZ.

Optimal**: Optimal dosing of the selected antibiotics based on the calculated CrCl.

Deficit***: Deficit dosing of the corresponding antibiotics was calculated by subtracting the prescribed dose from the optimal dose and consequently the %Deficit was obtained by dividing the deficit dosing over the prescribed dose.

1: Baseline.

2: Averages during admission.

BW: Body weight.

PIP/TAZ: Piperacillin/Tazobactam (Tazocin®).

MER: Meropenem (Meronem®).

IMI/CIL: Imipenem/Cilastatin (Tienam®).

PARA: Paracetamol.

BG: Blood glucose level.

cNa: Corrected sodium level.

HLOS: Hospital length of stay.

NA: Not-Applicable and statistically can't be computed.

Table 2 (Continued) Comparatively studied variables between Non-PIP/TAZ Cohort (Cohort I) and PIP/TAZ Cohort (Cohort II) among admitted COVID-19 infected patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021

Studied Comparative Variables	**Overall Cohorts (N=781) Mean±SD**	**Cohort I (Non-PIP/TAZ Cohort) (N=378,48.39%) Mean±SD**	**Cohort II (PIP/TAZ Cohort) (N=403, 51.61%) Mean±SD**	**Mean Differences ±SEM**	**P-Value**
%FCR $_{12}$	14.2%±17.8%	13.4%±17.4%	15.0%±18.2%	-1.6%±1.3%	0.204
%FER: ALB_{12}	-23.9%±28.1%	-24.5%±27.5%	-23.3%±28.6%	-1.3%±2.0%	0.531
%CRP: ALB_{12}	-34.7%±17.9%	-34.6%±18.2%	-34.7%±17.8%	0.1%±1.3%	0.964
%Δ WBC_{12}	14.7%±24.6%	15.0%±23.9%	14.5%±25.2%	0.5%±1.8%	0.786
%Δ TLC_{12}	239.7%±279%	243.1%±278.5%	236.4%±280.1%	6.7%± 20.0%	0.739
%Δ ANC_{12}	-8.9%±17.7%	-8.9%±17.9%	-8.9%±17.6%	0.0%± 1.3%	0.986
%Δ MC_{12}	-37.0%±21.6%	-37.6%±21.9%	-36.4%±21.3%	-1.2%± 1.5%	0.434
%Δ NLR_{12}	1765%±1384%	1735%±1375%	1794%±1393%	-58.9%± 99.1%	0.553
%Δ MLR_{12}	-69.6%±27.4%	-70.9%±26.3%	-68.4%±28.3%	-2.5%± 2.0%	0.210
%Δ (FER: ALB): LNR_{12}	-65.9%±34.4%	-67.2%±33.4%	-64.7%±35.3%	-2.6%±2.5%	0.297
%Δ (FER: ALB): LMR_{12}	-72.2%±33.8%	-73.8%±32.5%	-70.7%±34.9%	-3.1%± 2.4%	0.202
%Δ (CRP: ALB): LNR_{12}	-69.4%±44.1%	-67.6%±58.6%	-71.2%±23.5%	3.5%± 3.2%	0.262
%Δ (CRP: ALB): LMR_{12}	-76.0%±32.0%	-74.9%±42.1%	-77.1%±18.0%	2.2%± 2.3%	0.335

•Data results of the comparative variables between the Group I and Group II were statistically analyzed by independent T and One-Sample T-Test (at p-value< 0.05) and expressed as Mean±SD and Mean difference±SEM.

Cohort I: COVID-19 infected patients who were on Non-PIP/TAZ (Imipenem or Meropenem).

Cohort II COVID-19 infected patients who were on PIP/TAZ.

(FER: ALB) or (CRP: ALB) to inverse ratio of NLR or MLR (LNR or LMR, respectively) are a new proposed indicators by us that integrate two valid prognosticator ratios in one ratio in hopeful to improve the diagnostic and prognostic performance utility in COVID-19 infected patients.

FCR: Ferritin to CRP ratio.

FER: ALB: Ferritin to Albumin levels Ratio.

CRP: ALB: C-Reactive Protein to Albumin levels Ratio.

WBCs: White blood cells.

TLC: Total lymphocytes counts.

ANC: Absolute neutrophils count.

MC: Monocytes count.

NLR: Neutrophils to Lymphocytes ratio.

MLR: Monocytes to Lymphocytes ratio.

FER: Ferritin level.

ALB: Albumin level.

CRP: C-Reactive protein level.

LNR: Lymphocytes to Neutrophils Ratio.

LMR: Lymphocytes to Monocytes Ratio.

Table 3 Comparatively studied variables between Non-PIP/TAZ Cohort (Cohort I) and PIP/TAZ Cohort (Cohort II) among admitted COVID-19 infected patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021

	Cohort I (Non-PIP/TAZ) (N=378,48.39%)	Cohort II (PIP/TAZ) (N=403, 51.61%)	Overall Cohorts (N=781)	OD	χ 2 G 2 χ 2_Trend	p-Value
Gender						
F	118 (31.2%)	118 (29.3%)	236 (30.2%)	1.096 (95% CI; 0.81-1.49)	0.347 0.347 0.346	0.556
M	260 (68.8%)	285 (70.7%)	545 (69.8%)			
M: F	2.203: 1	2.415: 1	2.309:1			
COVID-19						
Suspected	117 (31.0%)	130 (32.3%)	247 (31.6%)	0.94 (95% CI; 0.69-1.27)	0.154 0.154 0.154	0.695
Confirmed	261 (69.0%)	273 (67.7%)	534 (68.4%)			
Severity Grade						
Mild/Moderate	197 (52.1%)	196 (48.6%)	393 (50.3%)	1.149 (95% CI; 0.87-1.52)	0.946 0.946 0.944	0.331
Severe/Critical	181 (47.9%)	207 (51.4%)	388 (49.7%)			
LDH: AST1						
<6.5	199 (52.6%)	193 (47.9%)	392 (50.2%)	1.21 (95% CI; 0.91-1.60)	1.764 1.765 1.762	0.184
≥6.5	179 (47.4%)	210 (52.1%)	389 (49.8%)			
cNa+						
<140	378 (100.0%)	248 (61.5%)	626 (80.2%)	0.39 (95%CI; 0.36-0.44)	181.38 241.27 181.15	0.00*
≥ 140	0 (0.0%)	155 (38.5%)	155 (19.8%)			
Mortality						
Survivors	309 (81.7%)	317 (78.7%)	626 (80.2%)	1.215 (95% CI; 0.85-1.73)	1.168 1.170 1.166	0.280
Non-Survivors	69 (18.3%)	86 (21.3%)	155 (19.8%)			

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage).

Cohort I: COVID-19 infected patients who were on Non-PIP/TAZ (Imipenem or Meropenem).

Cohort II COVID-19 infected patients who were on PIP/TAZ.

The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The likelihood-ratio chi-square statistic (G 2) is based on the ratio of the observed to the expected frequencies.

*: Significant (P-Value <0.05). N: Number of tested COVID-19 infected patients. F: Female. M: Male. M: F: Male to Female ratio.	cNa: Sodium level after correction with BG. MORT: Mortality rate. LDH: AST 1: Lactate dehydrogenase to aspartate transaminase ratio

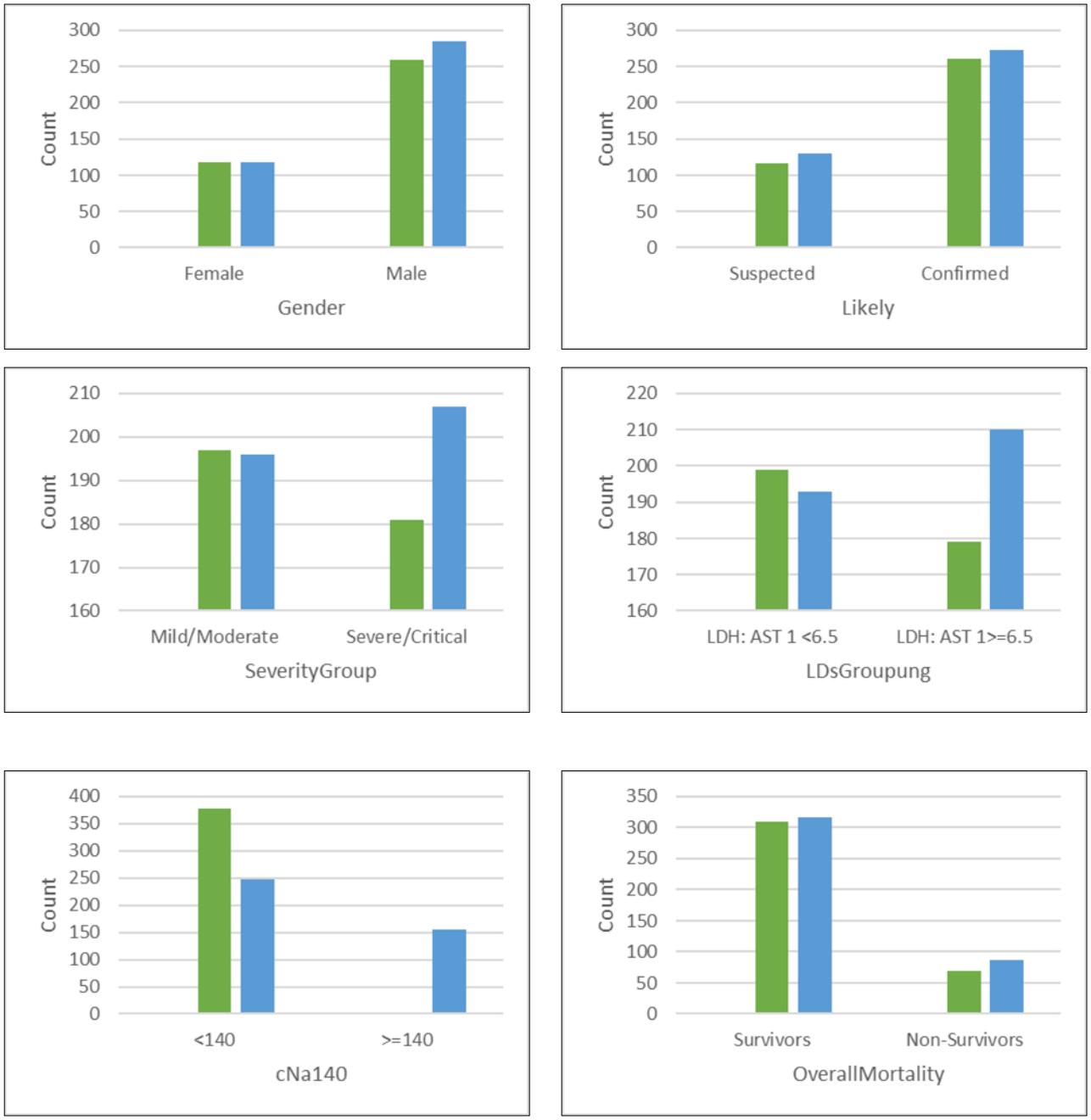

Figure 1 Bar charts' visualizations for comparatively studied patient's variables between Non-PIP/TAZ Cohort (Cohort I, Green Color) and PIP/TAZ Cohort (Cohort II, Blue Color)

Table 4 Comparatively studied variables between Non-PIP/TAZ Cohort (Cohort I) and PIP/TAZ Cohort (Cohort II) among admitted COVID-19 infected patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021.

	Cohort I (Non-PIP/TAZ) (N=378,48.39%)	**Cohort II (PIP/TAZ) (N=403, 51.61%)**	**Overall Cohorts (N=781)**	**OD**	**χ 2 G 2 χ 2_Trend**	**p-Value**
Dex						
Non-Dex	181 (47.9%)	195 (48.4%)	376 (48.1%	0.98 (95% CI; 0.74-1.29)	0.020 0.020 0.020	0.888
Dex	197 (52.1%)	208 (51.6%)	405 (51.9%)			
Ventilation						
NIMV	295 (78.0%)	308 (76.4%)	603 (77.2%)	1.096 (95% CI; 0.78-1.53)	0.289 0.289 0.289	0.591
IMV	83 (22.0%)	95 (23.6%)	178 (22.8%)			
Oxygen Therapy						
None	90 (23.8%)	87 (21.6%)	177 (22.7%)	NA	0.665 0.665 0.524	0.881
NC (3-6 L/min)	107 (28.3%)	116 (28.8%)	223 (28.6%)			
NIMV	98 (25.9%)	105 (26.1%)	203 (26.0%)			
IMV	83 (22.0%)	95 (23.6%)	178 (22.8%)			
Pathogens						
Non-Isolated	115 (30.4%)	138 (34.2%)	253 (32.4%)	NA	5.068 5.075 0.001	0.887
Acinetobacter	25 (6.6%)	24 (6.0%)	49 (6.3%)			
E. Coli	40 (10.6%)	34 (8.4%)	74 (9.5%)			
Klebsiella	26 (6.9%)	24 (6.0%)	50 (6.4%)			
Enterobacter	22 (5.8%)	22 (95.5%)	44 (5.6%)			
Proteus	21 (5.6%)	24 (6.0%)	45 (5.8%)			
Serratia	31 (8.2%)	27 (6.7%)	58 (7.4%)			
Morganella	30 (7.9%)	25 (6.2%)	55 (7.0%)			
Providencia	23 (6.1%)	25 (6.2%)	48 (6.1%)			
Citrobacter	24 (6.3%)	33 (8.2%)	57 (7.3%)			
Pseudomonas	21 (5.6%)	27 (6.7%)	48 (6.1%)			

Data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage).

Cohort I: COVID-19 infected patients who were on Non-PIP/TAZ.

Cohort II COVID-19 infected patients who were on PIP/TAZ.

The Pearson chi-square statistic (χ 2) involves the squared difference between the observed and the expected frequencies. The likelihood-ratio chi-square statistic (G 2) is based on the ratio of the observed to the expected frequencies.

NA: Not-Applicable and statistically can't be computed.

Dex: Dexamethasone.	02: Oxygen.
PIP/TAZ: Piperacillin/Tazobactam (Tazocin®).	NC: Nasal Canula on Oxygen flow rate of 3-6 L/min.
MER: Meropenem (Meronem®).	NIMV: Non-Invasive Mechanical Ventilation.
IMI/CIL: Imipenem/Cilastatin (Tienam®).	IMV: Invasive Mechanical Ventilation.

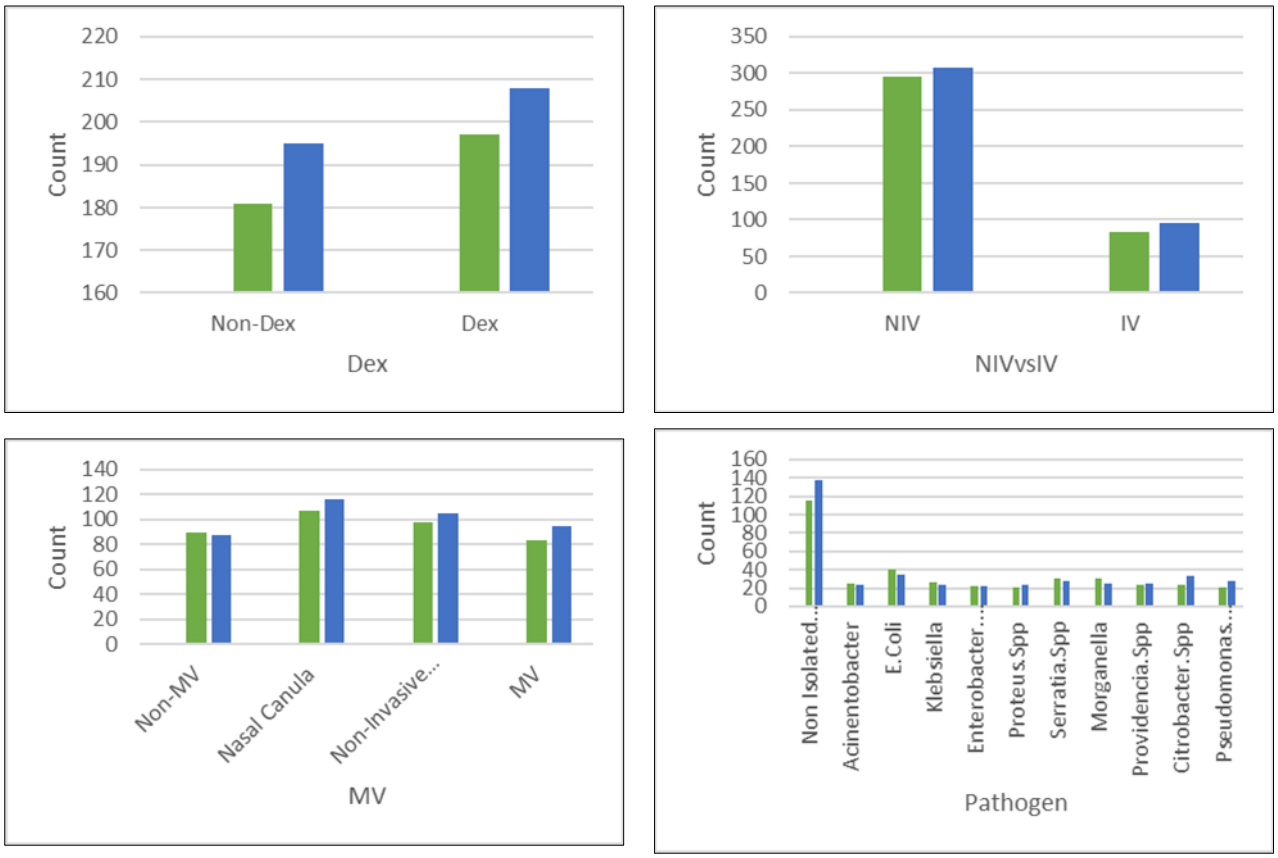

Figure 2 Bar charts' visualizations for comparatively studied patient's variables between Non-PIP/TAZ Cohort (Cohort I, Green Color) and PIP/TAZ Cohort (Cohort II, Blue Color)

Table 5 The optimal cut-off points, sensitivities, specificities, positive and negative predictive values, Youden and accuracy indices, and the negative likelihood ratios for cNa 2 and %Δ Na 12 for the overall COVID-19 infected patients' mortality

Prognostic Indicator	**Cut-off**	**TPR**	**FPR**	**YI**	**TNR**	**PPV**	**NPV**	**NLR**	**AI**
cNa $_2$ (mEq/l)	133.85	100.00%	11.02%	88.98%	88.98%	69.20%	100.00%	0.00%	91.17%
%Δ Na $_{12}$	1.95%	99.35%	5.43%	93.92%	94.57%	81.91%	99.83%	0.68%	95.52%
Sensitivity analysis was processed on total of 781 processed cases, 155-case was processed as positive actual state, and 626-case was processed as a negative actual state. 0 processed cases were dealt with as missing data. Smaller values of the test result variable(s) indicate stronger evidence for a positive actual state. The positive actual state is Non-Survivors. cNa $_2$ (1st tested prognosticator): Average corrected Sodium concentration after correction with blood glucose level during admission. %Δ Na $_{12}$ (2nd tested prognosticator): Changes in Sodium concentrations from baseline.									
TPR: True positive rate (sensitivity). FPR: False positive rate. YI: Youden index. TNR: True negative ratio (specificity).				PPV: Positive predictive value. NPV: Negative predictive value. NLR: Negative likelihood ratio. AI: Accuracy index.					

The area under the ROC curves (AUROC) of our tested prognosticator is fully illustrated in Fig 3. Table 5 shows the optimal cut-off point, TPR, TNR, YI, PPV and NPV, NLR, and AI, for our investigated prognosticators According to our study, the best cut-off values for the tested novel prognosticator were 133.85 mEq/l and 1.95%, respectively.

4. Discussion

This retrospective cohort study of 781 eligible inpatients with COVID-19 disease. Concerning the prognostic impact of low serum sodium in COVID-19, this study showed that hyponatremia during hospital admission was insignificantly related to LOS and overall mortality across the two studied cohorts. Oppositely, when we conducted the overall averaged corrected sodium concentrations (cNa_2) in the ROC test regarding overall 28-day SARS-CoV-2 infected patients mortality, we explored a significantly high AUROC for the two tested sodium-based mortality prognosticators which were significantly higher in $\%\Delta Na_{12\,vs}\,cNa_2$ With AUROC ±SEM (95% CI; Range) of 0.968±0.006 (95% CI; 0.956-0.980) vs 0.978±0.008 (95% CI; 0.966-0.986).

Contrary to the independent association of hyponatremia with mortality in pneumonia [23-25], our study did not identify hyponatremia as an unadjusted independent predictor of mortality in patients with COVID-19. We explored that the performances utilities of the two tested prognosticators were 100%, 88.98%, 88.98%, 69.20%, and 91.17% vs 99.35%, 93.92%, 94.57%, 81.91%, and 95.52% for sensitivities, Youden index, specificities, positive predictive values, accuracies.

The significant changes in Na^+ during antibiotics administration were likely from β-lactam ABs. Meropenem has the highest Na^+ load of the most common tested β-lactam ABs (3.92 mEq Na^+ /g AB) followed by Imipenem/Cilastatin (3.2 mEq Na^+/g AB) and Piperacillin/Tazobactam (2.51 mEq Na^+/g AB) and finally Cefepime with zero mEq Na^+ load due to its hydrochloride salt. In our study, we showed that the greatest hyponatremia mitigation positive effects were in Piperacillin/Tazobactam patients' group. These contrary results can be explained by the higher mg basis dose regimens of Piperacillin/Tazobactam's Na load inputs. To calculate AB Na^+ input (mEq Na^+/day), we multiplied AB Na^+ load (mEq Na^+ /g AB) by AB dose input (g AB/day).

5. Conclusion

Piperacillin/Tazobactam antibiotics administration in SARS-CoV-2 infected patients may have a non-antibiotic mortality benefit via its clinically significant propensity to mitigate the risk of hyponatremia-related negative clinical consequences, including mortality.

Compliance with ethical standards

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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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