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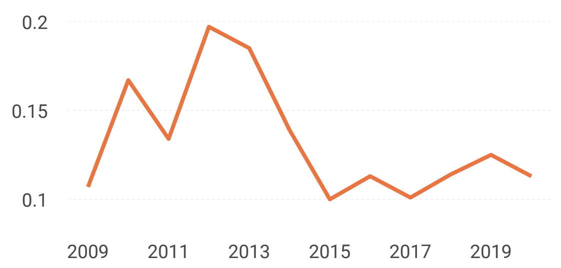

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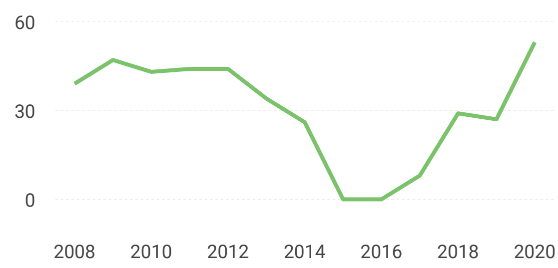

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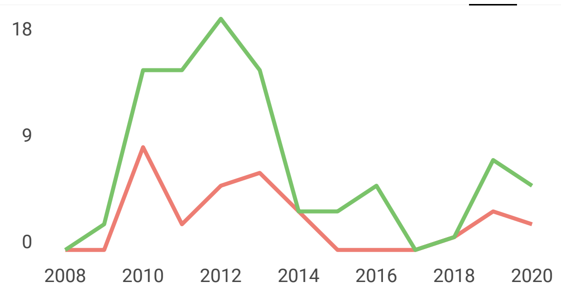

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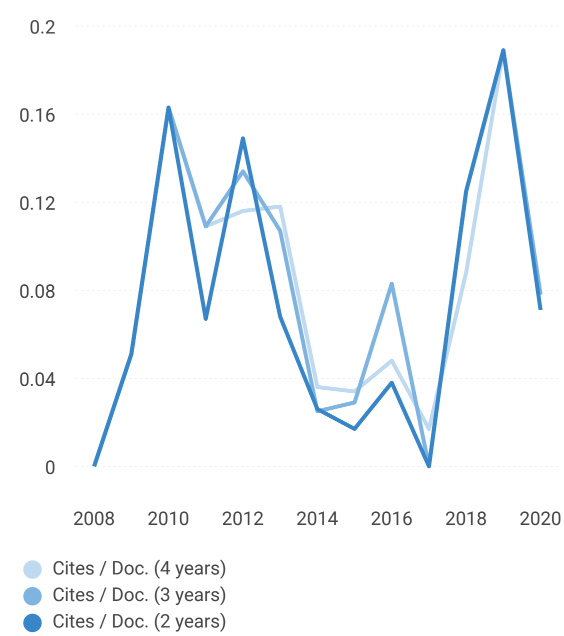

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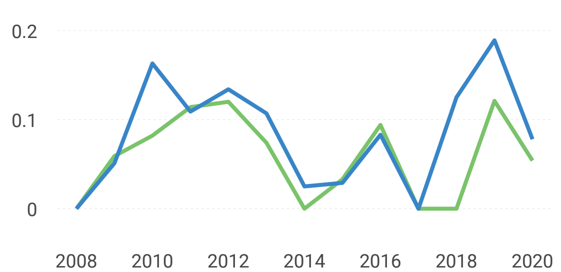

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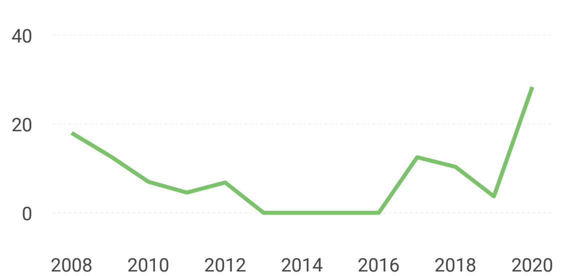

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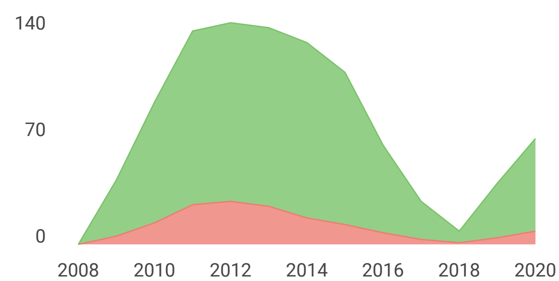

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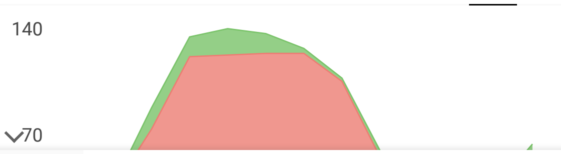

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DE CARACAS

Fundada el 13 de marzo de 1893

por el

DR. LUIS RAZETTI

Organo de la Academia Nacional de Medicina
y del Congreso Venezolano de Ciencias Médicas

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Julio - Septiembre 2022

Caracas - Venezuela

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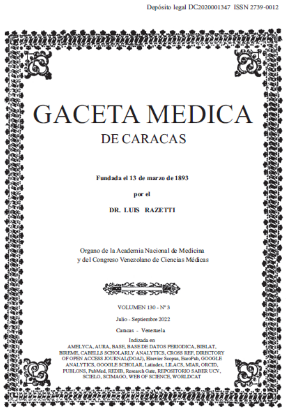
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Trends of Serum Electrolyte Levels toward Severity Rates in COVID-19 Patients with Type 2 Diabetes Mellitus Comorbidity in Dr. Soetomo Hospital Surabaya

Tendencias de los niveles de electrolitos séricos hacia las tasas de gravedad en pacientes con COVID-19 con comorbilidad de diabetes mellitus tipo 2 en el Hospital Dr. Soetomo Surabaya

Hamidah[1], Soebagijo Adi Soelistijo[1*], Erwin Astha Triyono[1], Agung Pranoto[1], Muhammad Miftahussurur[2,3*]

SUMMARY

Background: *Coronavirus Disease 2019 (COVID-19) causes a lot of morbidity and mortality. More than three-quarters of hospitalized patients experience complications in the kidneys such as acute kidney injury, proteinuria, hematuria, and electrolyte imbalance. The study addressed to get an overview of the profile of serum electrolyte levels and the severity trend of COVID-19 patients with comorbid Type 2 Diabetes (DM) at Dr. Soetomo Hospital, Surabaya.* **Methods:** *This retrospective descriptive study used secondary data from medical records of COVID-19 patients with Type 2 diabetes mellitus comorbid at Dr. Soetomo Hospital, Surabaya period April – September 2020.* **Result:** *Our study revealed 103 patients with COVID-19 with Type 2 DM comorbidity. The proportion of COVID-19 patients with comorbid Type 2 DM in Dr. Soetomo Hospital, Surabaya is 17.03 %. The percentage of patients with hyponatremia, normonatremia, hypernatremia, hypokalemia, normokalemia, hyperkalemia, hypochloremia, normochloremia, hyperchloremia were 52.48 %, 45.54 %, 1.98 %, 29.7 %, 49.5 %, 20.79 %, 33.33 %, 61.62 %, 5.05 %, respectively. There found 32 % of patients with COVID-19 with mild symptoms, 18.4 % moderate, 20.4 % severe, and 29.1 % critical. The critical severity case increases in hyponatremia, hypokalemia, and hypochloremia conditions.* **Conclusion:** *The severity of COVID-19 in patients with comorbid Type 2 DM is influenced by the laboratory values and the electrolyte change. The elevated*

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laboratory values and the decreased electrolyte levels followed by the increased severe COVID-19 case.

Keywords: *Serum electrolyte, COVID-19, Type 2 diabetes mellitus, hyponatremia, hypokalemia, hypochloremia*

RESUMEN

Antecedentes: *La enfermedad por coronavirus 2019 (COVID-19) causa mucha morbilidad y mortalidad. Más de las tres cuartas partes de los pacientes hospitalizados experimentan complicaciones en los riñones, como lesión renal aguda, proteinuria, hematuria y desequilibrio electrolítico. El estudio se dirigió a obtener una descripción general del perfil de los niveles de electrolitos séricos y la tendencia de gravedad de los pacientes con COVID-19 con diabetes tipo 2 (DM) comórbida en el Hospital Dr. Soetomo, Surabaya.* **Métodos:** *Este estudio descriptivo retrospectivo utilizó datos secundarios de registros médicos de pacientes con COVID-19 con diabetes mellitus tipo 2 comórbida en el Hospital Dr. Soetomo, Surabaya, período de abril a septiembre de 2020.* **Resultado:** *Nuestro estudio reveló 103 pacientes COVID-19 con comorbilidad de DM tipo 2. La proporción de pacientes con COVID-19 con DM tipo 2 comórbida en el Hospital Dr. Soetomo, Surabaya es del 17,03 %. El porcentaje de pacientes con hiponatremia, normonatremia, hipernatremia, hipopotasemia, normopotasemia, hiperpotasemia, hipocloremia, normocloremia, hipercloremia fueron 52,48 %, 45,54 %, 1,98 %, 29,7 %, 49,5 %, 20,79 %, 33,33 %, 61,62 %, 5,05 %, respectivamente. Se encontró un 32 % de pacientes COVID-19 con síntomas leves, un 18,4 % moderados, un 20,4 % graves y un 29,1 % críticos. El caso de gravedad crítica aumenta en condiciones de hiponatremia, hipopotasemia e hipocloremia.* **Conclusión:** *Las alteraciones de los electrolitos séricos como hiponatremia, hipopotasemia, hipocloremia, hiperpotasemia e hipercloremia contribuyen a aumentar los niveles de casos y gravedad en pacientes con COVID-19 con DM tipo 2 comórbida en el Hospital Dr. Soetomo Surabaya.*

Palabras clave: *Electrolito sérico, COVID-19, diabetes mellitus tipo 2, hiponatremia, hipopotasemia, hipocloremia.*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in December 2019 and has spread widely in the world. On 29 October 2020, World Health Organization (WHO) reports 44 351 506 globally confirmed cases of COVID-19 including 1 171 255 deaths. The fatality rate for COVID-19 has been estimated to be 0.5 %-1.0 % (1). The fact showed more than three-quarters of individuals hospitalized with COVID-19 experience complications in the kidney organs such as acute kidney injury, proteinuria, hematuria, and electrolyte imbalance. A meta-analysis revealed that lower sodium, potassium, and calcium concentrations were associated with severe disease (2).

The abnormal sodium levels are a risk factor for poor prognosis in COVID-19 patients. Hypernatremia conditions give 3.5 more times (95 % CI; 1.34-3.45; P = 0.0011) risk of death compared with normonatremia (3). Meanwhile, a study in France found that hyponatremia and hypokalemia were associated with COVID-19 with an odds ratio of 1.89 [95 % CI 1.24-2.89] and 1.76 [95 % CI 1.20–2.60], respectively (4). In many viral diseases, electrolyte imbalance especially hypokalemia has significant clinical implications in patient management and contributes to the mechanism of COVID-19 pathogenesis. Hypokalemia is able to make worse acute respiratory distress syndrome (ARDS) and myocardial injury, which are common complications of COVID-19, especially in patients with pulmonary or cardiac disease. This appears to be mediated by excessive activation of the Renin-Angiotensin-Aldosterone (RAA) system due to the binding of the SARS-CoV-2 virus to Angiotensin Converting Enzym 2 (ACE2) which results in a decrease in the amount of active ACE2 protein (5,6).

Type 2 DM is one of the most common comorbid diseases found in COVID-19 patients. A meta-analysis study revealed DM, age, and hypertension are the risk factor for the severity and mortality of COVID-19 in addition to obesity (7). Type 2 DM is a disease that causes electrolyte balance disorders such as hyponatremia, hyperkalemia, and hypomagnesemia (8). Hyponatremia, hypomagnesemia, and hypocalcemia are associated with more severe COVID-19 and require ICU care (6,9,10). Type 2 DM tends to cause hyperkalemia more often due to redistribution into the intravascular fluid, whereas

COVID-19 causes hypokalemia due to increased excretion of K^+ through urine (5,8,11) 2020. Electrolyte imbalances that occur in COVID-19 patients with comorbid Type 2 DM have the potential to increase the risk of death or more severe COVID-19 disease (12).

Electrolyte balance has an important role in the course of COVID-19 disease with comorbid Type 2 DM. If the patient does not receive adequate therapy, it can increase in severity to death. In addition, there are only a few studies in Indonesia regarding the evaluation of electrolyte imbalance status and its effect on survival and disease severity. Therefore, the researchers aimed to conduct a study on the description of serum electrolyte levels and their tendency to the severity of COVID-19 patients with comorbid type 2 DM in Dr. Soetomo Hospital, Surabaya.

METHODS

Study Design and Participant

This research was a descriptive retrospective study using secondary data from medical records. We involved all medical records of hospitalized patients with COVID-19-Type 2 DM comorbid who were treated at Dr. Soetomo Hospital, Surabaya the period April to September 2020 which met the inclusion and exclusion criteria. The inclusion criteria in this research involved male and female gender; age 18 – 80 years old; confirmed cases of COVID-19; have comorbid type 2 DM whereas the exclusion criteria are patients with Type 1 DM comorbid.

Serum electrolyte levels

Serum electrolytes that are taken and identified in this study are the levels of sodium, potassium, and chloride listed on the results of laboratory tests at the beginning of hospital admission. The normal reference value of sodium is 126-145 meq/L, potassium is 3.5-5.0 meq/L, and chloride is 95-107meq/L. Hypernatremia is defined as serum sodium >145 meq/L; hyponatremia when condition <126 meq/L. The reference range of hyperkalemia is >5.0 meq/L; hypokalemia is <3.5 meq/L. The serum chloride is categorized as hypochloremia in values>107meq/L and hypochloremia in <95meq/L.

Type 2 Diabetes Mellitus

Type 2 DM was defined according to the *Perkeni* diagnostic criteria check: fasting plasma blood glucose 126 mg/dL, plasma blood glucose 200 mg/dL 2 hours after oral glucose tolerance test, blood glucose 200 mg/dL with classic complaints, HbA1c more than 6.5 % using standardized tests. The subjects of research are including having type 2 DM if one of the results of the examination is met. The results of the examination were obtained at the initial admission to the hospital which was seen in the medical record.

COVID-19

A patient is categorized to be confirmed COVID-19 if there is a positive result at least once on the *rt*-PCR laboratory examination for SARS-CoV-2. The results of the examination were obtained when the subject was hospitalized as seen in the medical record. The severity of COVID-19 in subjects is classified into 4 categories: light, moderate, severe, and critical (13).

Statistical Analysis

Analysis data of this study using the Statistical Product Service Solution (SPSS) 25.0 program. The quantitative data will be written in mean ± standard deviation or median and interquartile range (IQR or interquartile range). The qualitative scale was obtained from the statistics of the frequency distribution. To determine the trend of electrolyte disturbances with respect to the severity of COVID-19 the *Chi-square* adjusting for trend test was used.

RESULTS

Patient's Characteristics of COVID-19 with Type 2 DM

In this present study, we collected 605 samples and found a total of 103 (17.03 %) samples confirmed positive for COVID-19 with comorbid

Type 2 DM. As shown in Table 1, we can identify that total COVID-19 in comorbid Type 2 DM patients is majority found in the age range 50-60 (54.40±2.46). Based on gender characteristics, the number of female patients is higher than male patients (58.3 % vs 41.7 %). A total of 82 samples report they consume DM drugs. Most of them used a combination of long-acting and short-acting insulin; there were 53 (63.41 %) patients. The majority of COVID-19 patients with comorbid Type 2 DM did not require hemodialysis with a percentage of 94.17 % or as many as 97 patients. Meanwhile, a total of 6 patients or 5.83 % of the sample required routine hemodialysis before treatment in a special isolation room.

Laboratory Characteristics of COVID-19 Patients with Type 2 DM Comorbidity

Researchers conducted a number of laboratory tests related to random blood sugar, HbA1c, SGOT/AST, SGPT/ALT, albumin, blood urea nitrogen (BUN), creatinine serum, and estimated glomerular filtration rate (eGFR) from COVID-19 patients with type 2 DM. The results can see in Table 2.

More than sixty percent of patients (61.05 %) have random blood sugar values ≥200 mg/dL. HbA1c levels are collected from 26 patients, be found twenty patients (76.90 %) have Hb1c levels ≥7 %. There are 72 patients (71.29 %) who have SGOT/AST levels >35 μ/L while SGPT/ALT levels of more than fifty percent of patients (54.46 %) are in the range of 0-45(μ/L). The albumin level of COVID-19 patients in this study is a low total of 89.89 % of patients have albumin value <3.5 g/dL. BUN and creatinine serum level of patients there is range 5-20 mg/dL (51.49 %) and 0.5-1.2 mg/dL (57.40 %), respectively. The kidney function of COVID-19 patients with comorbid type 2 DM based on eGFR showed a majority in level 60-89 ml/minutes (32.67 %).

Table 1

Characteristics of COVID-19 patients with comorbid Type 2 DM

	Frequency	%	Median	(Mean±SD)	Total
Age (Years)					102
21-30	1	0.98	25	-	
31-40	8	7.84	37	(36.75±2.92)	
41-50	25	24.51	46	(45.92 ±2.74)	
51-60	38	37.25	54	(54.40±2.46)	
61-70	22	21.57	64	(64.73±2.83)	
71-80	8	7.84	74.5	(74.38±2.88)	
Gender					103
Male	43	41.70	0	(0.00±0.00)	
Female	60	58.30	0	(0.00±0.00)	
DM Drug Use					82
Insulin long-acting	5	6.10	0	(0.00±0.00)	
Insulin short-acting	23	28.05	0	(0.00±0.00)	
Insulin long-acting and short-acting combination	52	63.41	0	(0.00±0.00)	
Insulin long-acting, short-acting, and metformin combination	1	1.22	0	(0.00±0.00)	
Metformin and Sulfonylurea combination	1	1.22	0	(0.00±0.00)	
Hemodialysis Status					103
Require Hemodialysis	6	5.83	0	(0.00±0.00)	
Not Require Hemodialysis	97	94,17	0	(0.00±0.00)	

Table 2

Laboratory Assessment Result of COVID-19 Patients with Type 2 DM Comorbidity

Laboratory Variable	Frequency	%	Median	(Mean±SD)	Total
Random Blood S ugar (mg/dL)					95
<70	4	4.21	49.5	(46.75±12.66)	
70-199	33	34.74	143.0	(138.39±36.60)	
≥200	58	61.05	270.5	(301.20±94.20)	
HbA1c (%)					26
<7	6	23.10	5.9	(5.78±1.05)	
≥7	20	76.90	10.5	(10.21±1.68)	
SGOT/AST (μ/L)					101
0-35	29	28.71	23.0	(24.17±7.04)	
>35	72	71.29	62.0	(75.49±46.22)	
SGPT/ALT (μ/L)					101
0-45	55	54.46	28.0	(27.64±9.98)	
>45	46	45.54	67.0	(78.48±35.45)	
Albumin (g/dL)					99
<3.5	88	89.89	3.0	(2.97±0.33)	
3.5 - 5.0	11	11.11	3.6	(3.62±0.12)	
BUN (mg/dL)					101
5-20	52	51.49	12.0	(12.24±3.57)	
>20	49	48.51	36.0	(49.96±37.06)	
Creatinine serum (mg/dL)					101
0.5-1.2	58	57.40	0.8	(0.84±0.20)	
>1.2	43	42.60	2.5	(4.98±4.80)	
eGFR (mL/minutes)					101
≥ 90	19	18.81	104.6	(119.70±33.64)	
60-89	33	32.67	72.9	(72.85±8.49)	
30-59	21	20.79	41.2	(43.28±9.74)	
15-29	11	10.89	22.0	(22.0±4.51)	
<15	17	16.83	6.2	(6.27±3.28)	

SGOT/AST: Serum Glutamic Oxaloacetic Transaminase/ Aspartate Aminotransferase; SGPT/ALT: Serum Glutamic Pyruvic Transaminase/ Alanine Aminotransferase; BUN: Blood Urea Nitrogen; eGFR: Estimated Glomerular Filtration Rate

The cross-tab analysis from the laboratory data and COVID-19 severity is arranged in Table 3. Based on the random blood sugar levels, the amount patients that have light, moderate, severe, and critical severity mostly have random blood sugar levels ≥200 mg/dL. The increase in random blood sugar levels follows by the increasing number of patients in each severity level. The critical severity was mostly found in the patients with high random blood sugar levels in fourteen patients compared with others: <70 mg/dL with only one patient and 70-199 mg/dL around thirteen patients.

The HbA1c levels data were collected from twenty-six patients and the majority have HbA1c levels ≥7 % (20 patients; 76.90 %) and the 30 % from it experienced light severity. There weren't

Table 3

Laboratory Data and the COVID-19 Severity

Laboratory Variable	**COVID-19 Severity** Light n (%)	Moderate n (%)	Severe n (%)	Critical n (%)	N
Random Blood Sugar (mg/dL)					
<70	0 (0.0)	2 (50.0)	1 (25.0)	1 (25.0)	4 (4.2)
70-199	10 (30.3)	3 (9.1)	7 (21.2)	13 (39.4)	33 (34.7)
≥200	20 (34.5)	13 (22.4)	11 (19.0)	14 (24.1)	58 (61.1)
N	30 (31.6)	18 (18.9)	19 (20.0)	28 (29.5)	95 (100.0)
HbA1c (%)					
<7	4 (66.7)	0 (0.0)	2 (33.3)	0 (0.0)	6 (23.1)
≥7	6 (30.0)	5 (25.0)	5 (25.0)	4 (20.0)	20 (76.9)
N	10 (38.5)	5 (19.2)	7 (25.9)	4 (15.4)	26 (100.0)
SGOT/AST (μ/L)					
0-35	13 (44.8)	5 (17.2)	5 (17.2)	6 (20.7)	29 (28.7)
>35	19 (26.4)	13 (18.1)	16 (22.2)	24 (33.3)	72 (71.3)
N	32 (31.7)	18 (17.8)	21 (20.8)	30 (29.7)	101 (100.0)
SGPT/ALT (μ/L)					
0-45	19 (34.5)	10 (18.2)	17 (30.9)	9 (16.4)	55 (54.5)
>45	13 (28.3)	8 (17.7)	4 (8.7)	21 (45.7)	46 (45.5)
N	32 (31.7)	18 (17.8)	21 (20.8)	30 (29.7)	101 (100.0)
Albumin (g/dL)					
<3.5	27 (30.7)	17 (19.3)	19 (21.6)	25 (28.4)	88 (88.9)
3.5 - 5.0	5 (45.5)	2 (18.2)	2 (18.2)	2 (18.2)	11 (11.1)
N	32 (32.3)	19 (19.2)	21 (21.2)	27 (27.3)	99 (100.0)
BUN (mg/dL)					
5-20	18 (35.5)	11 (21.6)	8 (15.7)	14 (27.5)	51 (50.5)
>20	14 (28.0)	8 (16.0)	12 (24.0)	16 (32.0)	50 (49.5)
N	32 (21.7)	19 (18.8)	20 (19.8)	30 (29.7)	101 (100.0)
Creatinine Serum (mg/dL)					
0.5-1.2	20 (34.5)	14 (24.1)	10 (17.2)	14 (24.1)	58 (57.4)
>1.2	12 (27.9)	5 (11.6)	10 (23.3)	16 (32.7)	43 (42.6)
N	32 (31.7)	19 (18.8)	20 (19.8)	30 (29.7)	101 (100.0)
eGFR (mL/minutes)					
≥ 90	6 (31.6)	4 (21.1)	2 (10.5)	7 (36.8)	19 (18.8)
60-89	13 (39.4)	10 (30.3)	5 (15.2)	5 (15.2)	33 (32.7)
30-59	4 (19.0)	3 (14.3)	7 (33.3)	7 (33.3)	21 (20.8)
15-29	1 (9.1)	2 (18.2)	3 (27.3)	5 (45.5)	11 (10.9)
<15	8 (47.1)	0 (0.0)	3 (17.6)	6 (35.3)	17 (16.8)
N	32 (31.7)	19 (18.8)	20 (19.8)	30 (29.7)	101 (100.0)

SGOT/AST: Serum Glutamic Oxaloacetic Transaminase/ Aspartate Aminotransferase; SGPT/ALT: Serum Glutamic Pyruvic Transaminase/ Alanine Aminotransferase; BUN: Blood Urea Nitrogen; eGFR: Estimated Glomerular Filtration Rate

found patients with moderate and critical severity on HbA1c levels <7 %. While in the HbA1c levels >7 %, the five patients have moderate, five patients got severe, and four patients in critical severity. The majority of patients have SGOT/AST levels of >35 μ/L (72; 71.3 %). The critical COVID-19 severity was dominantly found in patients with SGOT/AST levels >35 μ/L (21 patients), while on the 0-35 μ/L levels only six critical patients. Based on the SGPT/ALT levels, the critical patients were mostly found patients with SGPT/ALT levels >45 μ/L, and only nine critical patients that have SGPT/ALT levels of 0-45 μ/L. However, distinct from the SGOT/AST levels, the number of patients with light, moderate, and severe severity is higher than patients with SGPT/ALT levels of 0-45 μ/L.

The albumin levels on COVID-19 patients that low follows by a high number of patients with light and critical condition, there was twenty-seven and twenty-five patients, respectively. The majority of patients with albumin levels <3.5 g/dL have light severity. However, the critical patients dominantly have albumin levels <3.5 g/dL than 3.5-5.5 g/dL (25 vs 5). The number of patients with light severity dominant at the 5-20 mg/dl BUN levels (18 patients) and the high number of critical patients found in the BUN levels >20 mg/dL (16 patients). Overall, the number of patients at each severity level based on BUN value is not much different.

Based on the creatinine serum levels, the light patients mostly have creatinine serum levels of 0.5-1.2 mg/dL (20 patients;34.5 %) while, the creatinine levels serum >1.2 mg/dL followed by a high number of patients with critical severity (32.7 %). The total of subjects with *eGFR* <15 mL/minutes is seventeen and only three patients that on critical severity. The highest number of critical severity patients many were found at the *eGFR* levels ≥ 90 and 30-59 mL/minutes there were seven patients, respectively. The light patients mostly have *eGFR* levels of 60-89 mL/minute.

Serum Electrolyte and COVID-19 Severity Levels

The serum electrolyte levels, and severity of COVID-19 are shown in Table 4. Amount 53 patients (53.48 %) of 101 patients are hyponatremia. The normal condition was experienced by 46 patients and only two patients presented hypernatremia. Opposite to sodium level, 50 patients (49.50 %) have a normal range of potassium levels. Hypokalemia and hyperkalemia occurred in 30 (29.70 %) and 21 (20.79 %) patients. Same with potassium levels, chloride levels are dominated by patients that have a normal range (61.62 %). Hypochloremia is found in 33 (33.33 %) patients and hypochloremia only in 5 (5.05 %). Based on the level of COVID-19 severity, the number of patients with light and critical conditions is almost the same 33 (32.0 %) and 30 (29.1 %) whereas patients with severity levels of moderate and severe are 19 (18.4 %) and 21 (20.4 %), respectively.

Table 4

Distribution of Serum Electrolyte and COVID-19 Severity

Variable	**Frequency**	**%**	**Median**	**(Mean) ± (SD)**	**Total**
Sodium Level (mmol/L)					101
<135	53	52.48	130	(129.43) ± (4.98)	
135-145	46	45.54	139	(139.27) ± (3.47)	
>145	2	1.98	148	(148.06) ± (1.74)	
Potassium Level (mmol/L)					101
<3.6	30	29.70	3.25	(3.17) ± (0.38)	
3.6-5	50	49.50	4.20	(4.23) ± (0.39)	
>5	21	20.79	5.60	(5.78) ± (0.67)	
Chloride Level (mmol/L)					
99					
<95	33	33.33	93	(90.55) ± (6.25)	
95-107	61	61.62	99	(99.72) ± (3.07)	
>107	5	5.05	112	(141.60) ± (57.10)	
COVID-19 Severity					103
Light	33	32.03			
Moderate	19	18.44			
Severe	21	20.38			
Critical	30	29.12			

Trends of Severity of COVID-19 Patients with Comorbid Type 2 DM based on Serum Electrolyte Levels

Each elevated or reduced serum electrolyte levels have a different manifestation on the severity of corona disease. Figure 1 shows the number of patients with each severity level by category of serum electrolyte levels. There are nine categories of serum electrolyte levels and four categories for the severity of corona disease.

There was a significant difference in severity between hyponatremia and normal sodium (normonatremia) patients. Hyponatremia condition was dominated by critical patients (26/57) while normonatremia is dominated by light patients (22/42). Hypernatremia condition didn't show any influence on disease severity. Same with sodium levels, the reduction of potassium levels causes the number of critical patients to be increased (15/31) while with normal and high potassium levels more patients in light severity (16/49;10/21). Comparing the number of patients with hypochloremia and normal levels of chloride, we found that critical patients were higher in hypochloremia conditions (17 vs 11). The normal chloride serum is dominated by light patient severity.

Based on Figure 2a, at the normal serum sodium levels, there is no significant increase or decrease in the number of cases while hyponatremia has an increase in patients with critical severity. Based on the Chi-square test, there is a significant difference in sodium levels between hyponatremic patients and normal sodium patients ($P<0.001$). Figure 2b portrays the trend of severity in the category of hypochloremia compared to normochloremia. As with hypokalemia, under normal potassium conditions, there was also an increased case at each level of severity. There is a significant difference in serum potassium levels of hypokalemic patients and patients with normal potassium levels ($P=0.024$). Compared between hyperkalemia and normal levels of potassium (Figure 2c), the current study found that an increased case also occurred in normal potassium levels as in hyperkalemia. There is no significant difference in the level of potassium between

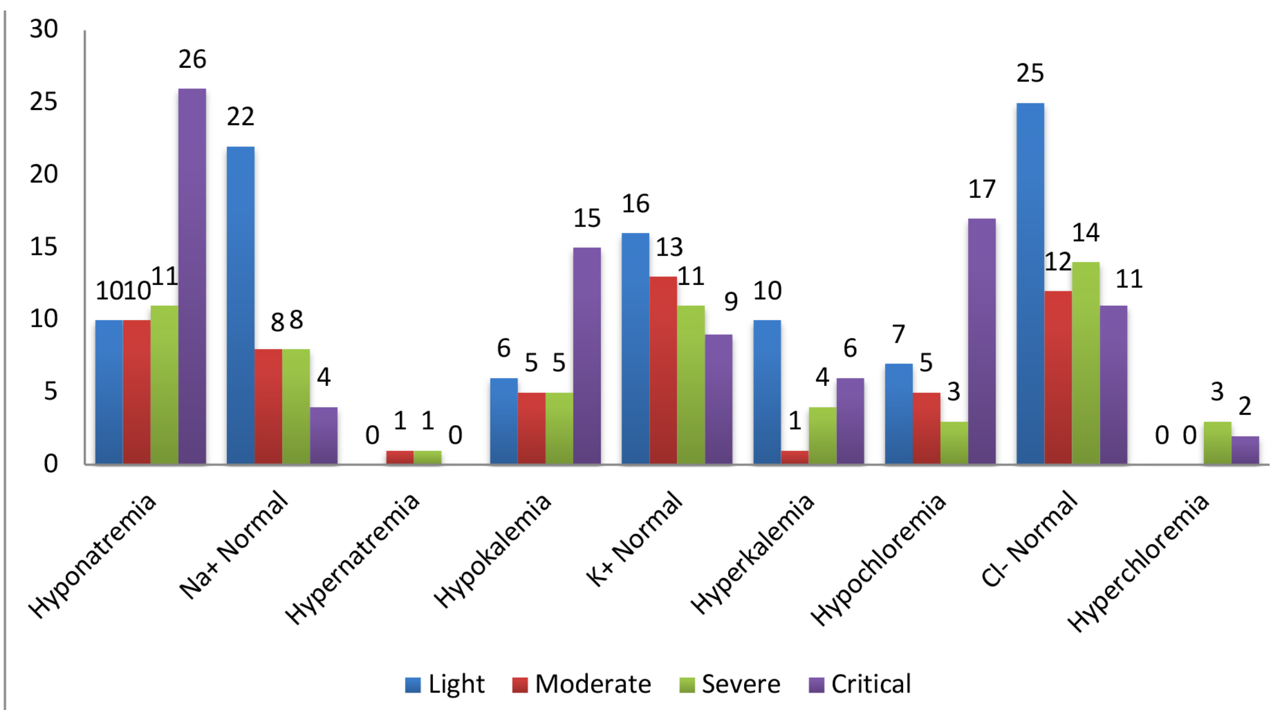

Figure 1. The number of patients' disease severity is based on electrolyte levels.

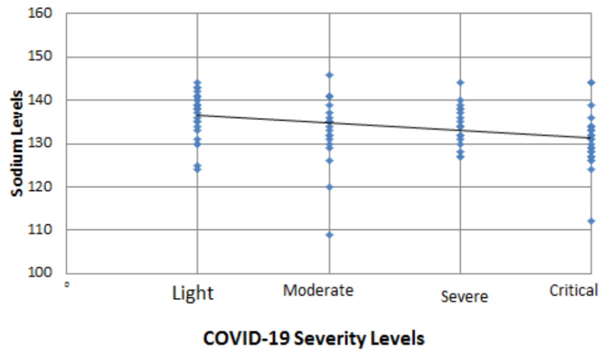

Figure 2**a**

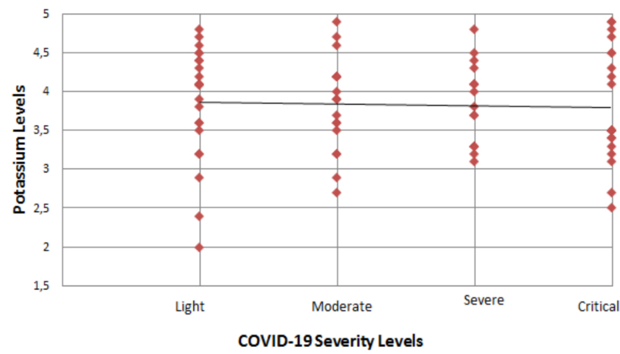

Figure 2**b**

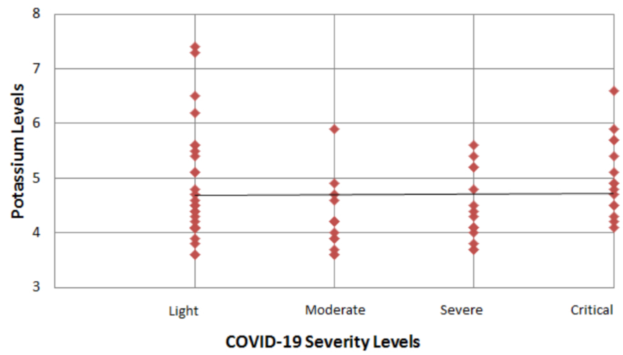

Figure 2**c**

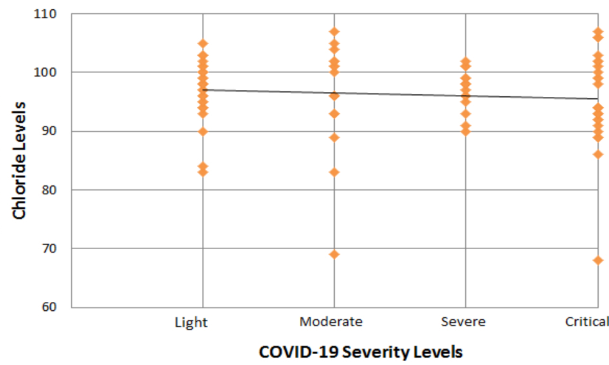

Figure 2**d**

Figure 2. Trends of COVID-19 Severity Levels towards Serum Electrolyte Levels; 2**a**) Hyponatremia-Normonatremia; 2**b**) Hypokalemia-Normokalemia; 2**c**) Hyperkalemia-Normokalemia; 2**d**) Hyperchloremia-Normochloremia with COVID-19 Severity Levels chart.

normal potassium patients with hyperkalemic patients (P=0.176). There was an increase in the number of cases from mild to critical severity in normal serum chloride levels as well as the hypochloremia patients (Figure 2d). Statistical analyses found that there is a difference in serum chloride levels between patients with normal chloride levels and those with low chloride levels (hypochloremia) (P=0.007).

DISCUSSION

Type 2 DM is one of the most common comorbidities in COVID-19. Research in Wuhan stated that 21.2 % of COVID-19 patients had comorbid Type 2 DM (14). Another study in Wuhan at Jinyintan Hospital found 19 % of COVID-19 patients with comorbid Type 2 DM which is the second most comorbid after hypertension (15). Type 2 DM increases mortality rates dramatically in COVID-19 and is an independent risk factor despite correction for age, race, gender, obesity, and hypertension (16). This is might due to an increase in D-dimer in COVID-19 patients with comorbid Type 2 DM, compared to those without Type 2 DM (15). A case report's result showed that in patients with COVID-19, the D-dimer level is fluctuating. The increase of D-dimer in COVID-19 cases is necessary to be monitored more seriously, it is related to the beginning of a cytokine storm, which causes worsening conditions in COVID-19 (17). There is a difference in the proportion of COVID-19 patients with comorbid Type 2 DM in this study with previous studies. This is possible because this study was only conducted in a special isolation room and didn’t include patients in the ICU.

Most COVID-19 patients with comorbid Type 2 DM are over 50 years old. Research at the University of Alabama found that 74.2 % of hospitalized patients were over the age of 50. Another study in Wuhan found that the average age of COVID-19 patients with comorbid Type 2 DM was over 50 years, which was 68.0 years (18). A previous study in Surabaya also found that the mean age of patients with COVID-19 is 50 ±14.6 SD. Additionally, age is a risk factor for patient mortality. Seventy percent of patients that died is they with aged over 50 years (19).

Most of the COVID-19 patients with comorbid Type 2 DM were female. Compared based on gender variable, the number of patients DM that female is dominant than male (40 vs. 23) (20). In the study of 74 patients with confirmed COVID-19 and Type 2 DM in Wuhan, the majority were women with a percentage of 51.4 %. Insulin therapy is the recommended therapy in the management of hyperglycemia in hospitalized COVID-19 patients with comorbid Type 2 DM. The recommended regimen for hyperglycemic patients previously taking oral anti-diabetic drugs or simply maintaining a diet may include intermittent subcutaneous regular insulin every six hours or rapid-acting insulin every four to six hours. However, in patients with persistent hyperglycemia, basal insulin is recommended (21).

Uncontrolled hyperglycemia has been implicated in increasing the severity of COVID-19 disease. COVID-19 causes disruption of endothelial cells through the enzyme ACE2 which is widely expressed in endothelial tissue. This causes an increase in angiotensin-II, causing vasoconstriction and cytokine release via endothelial activation. Endothelial cell dysfunction and microthrombus formation due to COVID-19 will be exacerbated by the microangiopathy that is already caused by diabetes. Meanwhile, disruption of the ACE-2 pathway by the coronavirus can also cause pancreatic beta-cell disruption resulting in hyperglycemia and worsening vasculopathy and coagulopathy (22,23). In hospitalized COVID-19 patients with diabetes, random blood sugar levels are expected to be in the range of < 10 mmol/L. A study showed that COVID-19 patients with comorbid Type 2 DM whose blood sugar levels were controlled between 3.9 and 10 mmol/L reduced the risk of death significantly (adjusted hazard ratio 0.14, 95 % confidence interval: 0.03-0.60) (21).

A cohort study in Wuhan found the mean HbA1c level was 7.5 % and stated that high HbA1c levels correlated with low blood SaO2 levels (r = -0.22, P = 0.01) (18). Diabetes can cause microvascular damage in the lungs, leading to a decrease in the diffusing capacity of carbon monoxide. This damage is directly correlated with HbA1c levels and the presence of other microvascular complications, such as diabetic neuropathy, retinopathy, and nephropathy. This occurrence is called "diabetic lung" and can lead to an increase in the severity of COVID-19 (21). The increase in SGOT and SGPT levels is probably affected by COVID-19 infection which can induce inflammation and liver injury. A retrospective study revealed that significant levels of ALT, AST, gamma-glutamyl transferase (GGT), and total bilirubin (TB) are elevated in severe COVID-19 patients compared with the mild patient (24). The use of multiple drugs, such as antibiotics, antivirals, antipyretics, and analgesics, and traditional Chinese medicine might cause liver injury in COVID-19 patients (25). The infection of COVID-19 also impaired liver function on protein synthesis and then decreased the albumin serum levels. The lower albumin levels are as known hypoalbuminemia. It is found mostly in severe COVID-19 patients than non-severe (26).

The other laboratory value that involved increasing the number of severe and critical patients was BUN. The elevation in BUN level is not only portrayed kidney dysfunction, but also reflects inflammatory status, catabolism, nitrogen equilibrium, and renal hypo-perfusion from hypovolemia, sepsis, or reduced cardiac output, many of which have been reported to be closely associated with adverse outcomes in COVID-19 patients (27,28). The increase of creatinine serum and decreased e-GFR value of patients also contributed to elevating the critical case. A recent study reported that serum creatinine elevation portends adverse prognostic significance in hospitalized patients with severe symptoms of COVID-19. There was found data that kidney function within 24 hours from admission is an independent factor for poor outcomes in a group of non-ICU-admitted patients with symptoms of COVID-19 (29). The decrease of the e-GFR consequence of hyperkalemia condition in diabetic patients. Its condition will reduce glomerular filtration of K+ and develop hyperkalemia due to hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis) (30,31).

The lower sodium levels were significantly associated with COVID-19 patients with severe symptoms (WMD: –0.91 mmol/L [95 % CI: –1.33 to –0.50 mmol/L]). This means that COVID-19 patients with severe symptoms can experience an electrolyte imbalance characterized by significantly low sodium levels (2). COVID-19 patients with comorbid Type 2 DM have a 4.67 times more risk of experiencing hyponatremia (32). Abnormal sodium levels are a risk factor for poor prognosis in COVID-19 patients. A French study found that hyponatremia was associated with COVID-19 with an odds ratio of 1.89 [95 % CI 1.24–2.89] (4). Hospitalized patients with COVID-19 and abnormal blood sodium levels have an increased risk of respiratory failure or death, and those with low sodium levels are twice as likely to require intubation or other advanced breathing apparatus than patients with normal sodium (3).

COVID-19 patients with severe symptoms may experience an electrolyte imbalance characterized by significantly low potassium levels (2). Hypokalemia has a close relationship with the prognosis in COVID-19 patients because it can trigger respiratory muscle dysfunction and ventricular arrhythmias it can affect the severity of the patient, the need for IMV (Intermittent Mandatory Ventilation), and lengthening hospitalization time (11). The binding of SARS-CoV-2 to ACE2 results in reduced counter-regulatory action in SRA. SARS-CoV-2 invades human cells by binding to angiotensin I converting enzyme 2 (ACE2) on the cell membrane. ACE2 is widely distributed in various types of tissues, especially in vital organs such as the heart, liver, kidneys, and lungs. ACE2 is known as the main mechanism of regulation of the renin-angiotensin system (RAS) axis which has an important role in controlling blood pressure and electrolyte balance. The effect that can be caused if there is a disturbance in the system is an increase in sodium and fluid reabsorption, causing an increase in blood pressure and potassium excretion (33).

Chloride is the main anion in the extracellular fluid. Chloride imbalance in the body's metabolism can cause metabolic acidosis. This happens because chloride binds a lot with other electrolytes in carrying out its role in maintaining the balance of acid-base levels in the body. A study of characteristics of COVID-19 patients in Wuhan in 2019 found a mean chloride level of 102.9 (34). A study in France found that the mean chloride level was 100 (97-104) mmol/L with 14.1 % of patients experiencing hypochloremia (4). Hypochloremia can develop acute myopericarditis with systolic dysfunction a week after the onset of fever and dry cough due to COVID-19 (35).

The limitation of this research is related to the result. Although the topic and the subject that be analyzed is DM type 2 patients, we didn't observe the correlation and pathogenesis between blood glucose levels and COVID-19 severity that might have reciprocity. This study didn't obtain the mortality rate of the patients, just observed the severity with higher status is critical. The factor of oxygen support didn't analyze in this study. It might affect the electrolyte levels.

CONCLUSION

The severity of COVID-19 in patients with comorbid Type 2 DM is influenced by the laboratory values and the electrolyte change. The elevated laboratory values and the decreased electrolyte levels followed by the increased severe COVID-19 case.

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