

Association of SARS-COV-2 Real-Time PCR Cycle Threshold (Ct) Values with the Clinical and Laboratory Profiles of Confirmed COVID-19 Patients Admitted in Tertiary Infectious Disease Hospital in Manila: A Retrospective Study

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ABSTRACT

Background and Objectives. COVID-19 has quickly spread over the world and became an unprecedented burden on health care systems. COVID-19 diagnosis necessitates the use of precise testing methods such as RT-PCR. This method is generally reported as positive or negative, however, studies have shown its semi-quantitative capability through Ct values. This study determined an association that exists between the Ct values, clinical features, and laboratory findings among COVID-19 patients admitted in a tertiary infectious disease hospital in Manila, Philippines. This attempts to further explore the utility of RT-PCR in disease severity classification and diagnosis.

Methods. This was an observational retrospective study that utilized a purposive sampling method, wherein patients were selected based on the DOH case definition of confirmed COVID-19, and were stratified according to disease severity. Baseline laboratory data of the patients were gathered from medical records covering the period of June 2021 to January 2022 using a Data Collection Form. Chi-square test was used to measure the degree of association between the groups and categorical variables. Regression Analysis was used to identify predictors for certain variables. SPSS Statistics for Windows, Version 25.0 was utilized for the statistical analysis.

Results. The total WBC, neutrophil, lymphocyte and monocyte counts, serum urea, LDH, CRP and PTT were found to be predictors of COVID-19 severity. There was no significant difference observed between the disease severity and the patient's clinical outcome. All routine laboratory tests that were taken at baseline (ORF Gene, N-Gene, Hematocrit, White Blood Cells, Neutrophil, Lymphocyte, Monocyte, Platelet Count, Urea, Creatinine, SGPT, SGOT, Na, K, LDH, Ferritin, C Reactive Protein, Procalcitonin, D-Dimer, PT, PTT) were not significant predictors of the clinical outcome. Although WBC, neutrophil, lymphocyte, and monocyte count, urea, LDH, CRP, and PTT were predictors of disease

severity. The study also reported that the odds of having severe to critical disease increases by 20.6% for every one unit increase in neutrophil count, and 17.4% for every one unit increase in lymphocyte count. Among the laboratory parameters, neutrophil count ($p=0.010654063$) and urea ($p=0.04149874$) have direct relationship with the N gene Ct values while Orf gene Ct Values have direct relationship with lymphocyte count ($p=0.01269027$). Similarly, regression showed that as monocyte count, creatinine levels, and serum ferritin decrease, Ct values increase. Sex was found to not be a significant predictor of disease severity and clinical outcome. There was also no significant difference observed between the disease severity and the patient's clinical outcome.



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Conclusion. The study showed that the Ct values for both ORF and N genes were not significant predictors of both disease severity and clinical outcome. However, ORF gene Ct values have direct relationship with lymphocyte counts while N gene Ct values have direct correlation with neutrophil count and urea levels. Similarly, monocyte, creatinine, and ferritin are negatively correlated with Ct values. It is important to monitor the patient's laboratory biomarkers in order to determine the proper course of treatment and management for each case.

Keywords: SARS-CoV-2, COVID-19, RT-PCR, Ct value, COVID-19 disease severity, COVID-19 laboratory findings

INTRODUCTION

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2), emerged in Wuhan (China) in December 2019, and was later named as Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO).^{1,2} The number of cases rapidly increased throughout the world, and the disease was declared a pandemic in March 2020.^{3,4} As of April 23, 2021, there are 971,049 COVID-19 confirmed cases and 16,370 died in the Philippines with most of its cases found in the National Capital Region.^{5,6} Most tests rely on the reverse transcription-polymerase chain reaction (RT-PCR) which is the gold standard for early detection of SARS-CoV-2 RNA.⁷ Manufacturers utilize a range of RNA gene targets, with most tests focusing on one or more of the envelope (env), nucleocapsid (N), spike (S), RNA-dependent RNA polymerase (RdRp), and ORF1 genes.⁸ Owing to the expensive test kits needed to monitor test results of patients with prolonged hospital stays, clinicians choose to interpret cycle threshold (Ct) values as they correlate with viral load. The cycle threshold (Ct) value is the number of amplification cycles required to reach a fixed background level of fluorescence at which the real-time PCR diagnostic result switches from negative to positive. This Ct value can be used to determine SARS-CoV-2 infectivity.⁹ A Ct value of <40 is considered positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹⁰ A lower Ct value suggests a high viral load concentration, whereas a high Ct value indicates a low genetic material concentration.^{11,12} Laboratories and clinicians utilize Ct values for the quantification of viral load, with limitations.¹³ Different laboratories might use slightly different Ct value thresholds to determine positivity, which could affect case counts and public health responses. This information brought on an unprecedented level of interest in the clinical utility of Ct values. Recent studies have linked Ct values and disease severity, and proposed these values to be considered in clinical decision-making.¹⁴⁻¹⁷ Aside from the Ct values, resources that are available must be utilized such as laboratory markers that can supplement additional information regarding patient care.¹⁸ Numerous laboratory biomarkers are used initially for COVID-19 infection prediction or diagnosis.

Lymphocytes, leukocytes, neutrophil count, prothrombin time and D-dimer, procalcitonin, C-reactive protein (CRP) levels, and serum ferritin. Biochemical factors including liver enzymes, kidney function tests, and lactate dehydrogenase parameters that may be altered in mild and severe COVID-19 cases.^{19,20} According to WHO, many aspects of the virus and disease have not been fully understood thus the relationship between viral concentration, biomarkers, and the disease severity need to be further evaluated.²¹

The aim of our study is to determine the association of the baseline RT-PCR Ct values with disease severity as per the Department of Health (DOH) classification together with baseline laboratory findings in confirmed COVID-19 patients upon their hospital admission.

MATERIALS AND METHODS

Ethical approval was obtained from the San Lazaro Hospital (SLH) Research Ethics Committee. This research protocol adheres to the ethical principles of the "International Guidelines for Ethical Review of Epidemiological Studies" described in the Council for International Organizations of Medical Sciences (CIOMS) since this involved the use of existing patient records containing biomedical or other information about individuals who may or may not be identifiable from the records or information. Confidentiality of data acquired from the anonymized patients was applied in compliance with RA 10173 (Data Privacy Act of 2012). Therefore, the use of such records and the protection of the confidentiality of data obtained from those records were strictly observed.

This study utilized a quantitative observational retrospective cohort design. Specifically, this determined the relationship of clinico-demographic factors, laboratory biomarkers, and disease severity to the Ct values among anonymized confirmed rRT-PCR COVID-19 positive patients admitted at San Lazaro Hospital (SLH) from June 2021 to January 2022. Moreover, the researchers looked into past data such as medical records and the laboratory records of COVID-19 patients to determine the relationship to their Ct values.

Data of anonymized patients who did not have nasopharyngeal/oropharyngeal swab samples collected and analyzed by rRT-PCR, in the hospital within one day of admission and those with insufficient medical records or laboratory data of anonymized patients (certain biomarkers missing, age not included, other clinico-demographic variables not demonstrated, etc.) or erroneously written (typographical errors, formatting errors, incorrect data type, nonsensical data, etc.) were excluded in the study. Asymptomatic cases were excluded because laboratory markers are either rarely or not requested for these sets of population (Figure 1).

The researchers utilized a purposive sampling method. The study team retrospectively collected the demographic and clinical profile of confirmed COVID-19 patients admitted in

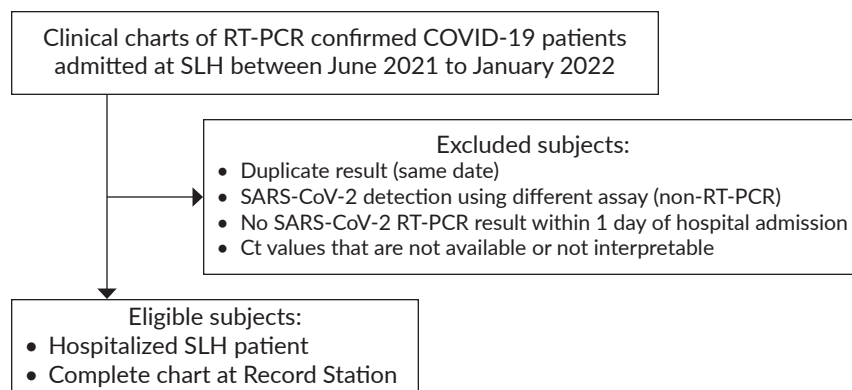


Figure 1. Flow diagram of patients included in the study and reasons for exclusion.

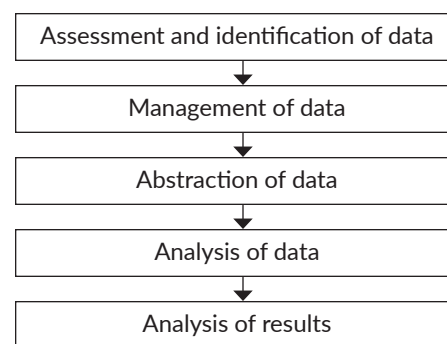


Figure 2. Flow chart showing the methods that will be utilized in our analysis.

a tertiary hospital in Manila from June 2021 to January 2022. RT-PCR testing for SARS-CoV-2 was performed upon admission using Sansure PCR kit and Seegene Allplex™ 2019-nCoV Assay, both with a <40 cutoff to be considered “detected” or “positive”. Sample collection was done through routine methods such as nasopharyngeal swab (NPS), oropharyngeal swab (OPS), or both. The levels of the viral nucleic acid from the extracted specimens of each confirmed COVID-19 patient upon their admission with their Ct values from RT-PCR assays were collected and gathered. The anonymization of the patient record was done by the medical records section prior to access of the researchers to their medical records. Asymptomatic patients were not tested for COVID-19, and were therefore excluded.

Clinical data including demographic background, comorbidities, manifestation, and laboratory parameters that were taken at baseline, as per request of the attending physician, were retrieved from the electronic medical records of the anonymized patients. According to the WHO guidelines, patients were stratified into groups based on age, as follows: 0–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and > 85 years. Disease severity was classified upon admission as follows: mild, moderate (hospitalization in the ward for observation and oxygen therapy), severe (hospitalization in the intensive care unit), critical, and discharge or death, also taking into consideration the DOH disease severity classification. The data was managed, stored, and analyzed using Data abstraction software packages such as Microsoft Access and MedQuest. These programs convert the data abstraction instrument into an electronic format that can be used for data entry, quality assurance, and data management (Figure 2). Data was also password-protected wherein only the researchers have access.

The collected data were anonymized by a non-member of the study team assigned in SLH Health Information Management Department (HIMD) based on a coding scheme devised. All study team members executed a Non-Disclosure and Confidentiality Agreement as required by

the SLH. The data collector utilized the Data Collection Form (S1). Erroneous values/data were stroked out, date of rectification/correction was written, and the initials of the corrector were affixed.

Continuous variables were described with mean $\pm$ standard deviation (SD) and compared with Student's *t* test or Mann-Whitney U test, as appropriate. Categorical parameters were noted in absolute numbers and percentage, and compared with the Chi2 test or the Fisher exact test. Principal component analysis was performed to obtain an overall idea of the data and the interrelationships among the different categorical variables. Statistical analysis was conducted using SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp) and SAS/STAT 10.1 (SAS Institute Inc., Cary, NC).

RESULTS

The characteristics of the patients were determined using descriptive statistics. Independent *t*-test was used to compare the mean values of dependent variables between the two clinical outcomes. Simple logistic regression was done to screen potential predictors of the clinical outcomes of patients. A series of binomial logistic regression analyses were performed and forward selection was used in order to determine the significant predictors of clinical outcome.

Univariate Analysis

Majority of the patients were females (Table 1). Majority of the specimens were obtained via oropharyngeal swab and were tested once for the duration of the patient's admission (Tables 2 and 3). Only 2.14% (9) of the patients have succumbed to death (Table 4).

Less than 5% (16) had mild disease and the majority of the patients (37.35%) had moderate disease. More than half had severe to critical disease (Table 5).

Table 6 presents the mean value of the results of laboratory tests commonly done among COVID-19 patients

which includes the detection of ORF and N genes done through RT-PCR, and the routine blood and coagulation tests, liver profile, kidney profile, and inflammation tests.

There was no significant difference observed between expired and discharged patients in terms of sex distribution (Table 7).

Table 1. Distribution of Confirmed COVID-19 Patients Admitted in San Lazaro Hospital according to Sex (N=423)

Sex	No.	(%)
Male	167	39.48
Female	256	60.52

Table 2. Distribution of Confirmed COVID-19 Patients Admitted in San Lazaro Hospital according to Specimen Type (N=422)

Specimen Type	No.	(%)
NPS	111	26.30
OPS	299	70.85
NPS/OPS	12	2.84

Table 3. Distribution of Confirmed COVID-19 Patients Admitted in San Lazaro Hospital according to Specimen Number (N=418)

Specimen Number	No.	(%)
1 st	291	69.83
2 nd	106	25.18
3 rd	16	3.80
4 th	1	0.24
5 th	1	0.24
6 th	1	0.24
7 th	2	0.48

Table 4. Distribution of Confirmed COVID-19 Patients Admitted in San Lazaro Hospital according to Clinical Outcome (N=420)

Specimen Number	No.	(%)
Discharged	411	97.86
Expired	9	2.14

Table 5. Distribution of Confirmed COVID-19 Patients Admitted in San Lazaro Hospital according to Severity (N=415)

Severity	No.	(%)
Mild	16	3.86
Moderate	155	37.35
Severe	91	21.93
Critical	153	36.87

There was also no significant difference observed between expired and discharged patients in terms of the severity of the patients' disease (Table 8).

Table 9 presents the result of regressing the clinical outcome with sex and disease severity as categorical variables. Simple logistic regression showed that sex and disease severity were not significant predictors of clinical outcome.

Table 6. Mean ($\pm$ Standard Deviation) of the Laboratory Tests' Results of Confirmed COVID-19 Patients Admitted in San Lazaro Hospital

Laboratory Markers	n	Mean	SD
ORF	374	28.982	0.342
N-Gene	418	28.250	0.346
Hematocrit (%)	422	0.382	0.003
White Blood Cells (cells/uL)	420	8.733	0.248
Neutrophil (%)	420	74.476	0.832
Lymphocyte (%)	420	17.927	0.693
Monocyte (%)	420	6.570	0.188
Platelet Count (cells/uL)	422	258.261	5.196
Urea (mg/dL)	406	6.371	0.244
Creatinine (mg/dL)	411	80.348	3.456
SGPT (iu/dL)	403	66.587	3.712
SGOT (iu/dL)	404	81.693	5.146
Na (mEq/L)	411	134.002	0.538
K (mEq/L)	411	4.048	0.084
LDH (iu/dL)	252	497.159	35.108
Ferritin (ng/dL)	119	1249.763	273.962
C-Reactive Protein (ug/dL)	241	81.446	4.698
Procalcitonin (ng/dL)	189	8.864	3.461
D-dimer (ug/L)	293	404.796	86.722
PT (sec)	325	14.720	0.255
PTT (sec)	320	37.143	0.552

Table 7. Comparison of Clinical Outcome between Sexes (N=420)

Sex	Clinical Outcome				p-value
	Expired		Discharged		
	No.	(%)	No.	(%)	
Male	8	3.15	246	96.85	0.078
Female	1	0.60	165	99.40	

Table 8. Comparison of Clinical Outcome across Severity of Disease (N=412)

Severity	Clinical Outcome				p-value
	Expired		Discharged		
	No.	(%)	No.	(%)	
Mild	0	0.00	16	100.00	0.222
Moderate	1	0.65	154	99.35	
Severe	2	2.20	89	97.80	
Critical	6	4.00	144	96.00	

Table 10 presents the result of regressing the clinical outcome with the laboratory parameters of the patients as continuous variables. Simple logistic regression showed that all laboratory tests listed in Table 6 were not significant predictors of the clinical outcome.

Table 11 presents the result of regressing the disease severity with sex as the categorical variable. Simple logistic regression showed that sex was not a significant predictor of disease severity.

Table 12 presents the result of regressing the disease severity with continuous variables. Simple logistic regression showed that white blood cell count, neutrophil count,

lymphocyte count, monocyte count, urea, LDH, C-Reactive Protein, and PTT were predictors of disease severity. For every one unit increase in white blood cell count, the odds of the occurrence of having severe to critical disease increases by 10.9%. For every one unit increase in neutrophil count, the odds of the occurrence of having severe to critical disease increases by 9.2%. For every one unit increase in lymphocyte count, the odds of the occurrence of having severe to critical disease decreases by 8.5%. For every one unit increase in monocyte count, the odds of the occurrence of having severe to critical disease decreases by 29.2%. For every one unit increase in urea, the odds of the occurrence of having

Table 9. Results of Logistic Regression of Clinical Outcome and Sex

Regressors	Unadjusted Odds Ratio	Confidence Interval	p-value
Sex (Reference: Female)			
Male	5.366	0.664 – 43.304	0.115
Disease Severity (Reference: Mild – Moderate)			
Severe – Critical	5.837	0.723 – 47.108	0.098

Table 10. Results of Logistic Regression of Clinical Outcome and Laboratory Parameters

Regressors	Unadjusted Odds Ratio	Confidence Interval	p-value
<i>ORF</i>	0.948	0.858 – 1.047	0.294
<i>N-Gene</i>	0.971	0.886 – 1.064	0.532
<i>Hematocrit (%)</i>	0.875	<0.001 – 22936.45	0.980
<i>White Blood Cells (cells/uL)</i>	1.022	0.904 – 1.156	0.734
<i>Neutrophil (%)</i>	1.048	0.984 – 1.117	0.091
<i>Lymphocyte (%)</i>	0.933	0.852 – 1.021	0.063
<i>Monocyte (%)</i>	0.846	0.675 – 1.061	0.147
<i>Platelet Count (cells/uL)</i>	0.995	0.986 – 1.002	0.186
<i>Urea (mg/dL)</i>	1.067	0.971 – 1.172	0.239
<i>Creatinine (mg/dL)</i>	0.998	0.984 – 1.013	0.808
<i>SGPT (iu/dL)</i>	0.993	0.974 – 1.012	0.370
<i>SGOT (iu/dL)</i>	0.996	0.981 – 1.011	0.520
<i>Na (mEq/L)</i>	1.002	0.936 – 1.073	0.953
<i>K (mEq/L)</i>	1.013	0.718 – 1.429	0.944
<i>LDH (iu/dL)</i>	0.998	0.994 – 1.002	0.341
<i>Ferritin (ng/dL)</i>	1.000	0.999 – 1.000	0.861
<i>C-Reactive Protein (ug/dL)</i>	0.993	0.979 – 1.001	0.350
<i>Procalcitonin (ng/dL)</i>	1.004	0.997 – 1.012	0.277
<i>D-dimer (ug/L)</i>	0.999	0.999 – 1.000	0.928
<i>PT (sec)</i>	0.985	0.805 – 1.206	0.874
<i>PTT (sec)</i>	0.978	0.896 – 1.068	0.608

Table 11. Results of Logistic Regression of Disease Severity and Sex

Regressors	Unadjusted Odds Ratio	Confidence Interval	p-value
Sex (Reference: Female)			
Male	1.393	0.935 – 2.076	0.103

severe to critical disease increases by 17.1%. For every one unit increase in LDH, the odds of the occurrence of having severe to critical disease increases by 0.6%. For every one unit increase in C-Reactive Protein, the odds of the occurrence of having severe to critical disease increases by 1%. For every one unit increase in PTT, the odds of the occurrence of having severe to critical disease increases by 5.4%.

Findings of the multiple logistic regression and forward variable selection were shown in Table 13. Some variables screened as predictor variables were not selected in the forward selection.

Table 14 shows the findings of the bivariate analysis of different variables against the N Gene. Using linear regression, the N Gene was placed in the x-axis for all instances while the other variable was placed in the y-axis. Outliers were identified as values with a standard error (a measure of the standard deviation of the errors) of three or more. These extreme values were promptly removed so as to not significantly affect the general relationship found between two variables. Upon further investigation, some

of these outliers are from patients that are diagnosed with underlying conditions prior to COVID-19 infection (i.e., tetanus infection, HIV). We have also observed multiple possible data entry errors that exceed x10 to x100 of mean values, suggesting that there could have been errors in decimal placement. Based on these results, two variables were identified as significant (p -value<0.05): Monocyte and Creatinine. Looking at the linear regression of monocyte and creatinine vs N gene, there will be a 0.117 unit decrease in monocyte count and a 1.3 unit decrease in creatinine levels for every unit increase of the N Gene variable.

Table 15 shows the findings of the bivariate analysis using correlation coefficient between the ORF gene Ct values and the laboratory profile of the patients. There were two observed variables deemed to have a significant linear correlation with the ORF gene: Ferritin and Monocyte. For every unit increase in the ORF Gene variable, there is a 0.117 unit decrease in monocyte count and a 55 unit decrease in ferritin levels.

Table 12. Results of Logistic Regression of Disease Severity and Laboratory Parameters

Regressors	Unadjusted Odds Ratio	Confidence Interval	p-value
ORF	0.970	0.939 – 1.0001	0.058
N-Gene	0.986	0.959 – 1.014	0.326
Hematocrit (%)	14.909	0.899 – 247.022	0.059
White Blood Cells (cells/uL)	1.109	1.056 – 1.165	<0.001*
Neutrophil (%)	1.092	1.073 – 1.111	<0.001*
Lymphocyte (%)	0.915	0.897 – 0.934	<0.001*
Monocyte (%)	0.708	0.659 – 0.761	<0.001*
Platelet Count (cells/uL)	1.001	0.999 – 1.002	0.295
Urea (mg/dL)	1.171	1.090 – 1.257	<0.001*
Creatinine (mg/dL)	1.001	0.998 – 1.004	0.471
SGPT (iu/dL)	1.001	0.998 – 1.004	0.339
SGOT (iu/dL)	1.003	0.999 – 1.005	0.053
Na (mEq/L)	1.000	0.982 – 1.018	0.973
K (mEq/L)	1.034	0.900 – 1.188	0.635
LDH (iu/dL)	1.006	1.003 – 1.008	<0.001*
C Reactive Protein (ug/dL)	1.010	1.006 – 1.015	<0.001*
Procalcitonin (ng/dL)	0.997	0.991 – 1.003	0.427
D-dimer (ug/L)	1.000	0.999 – 1.000	0.462
PT (sec)	1.028	0.960 – 1.100	0.433
PTT (sec)	1.054	1.020 – 1.089	0.002*

Table 13. Results of Multiple Logistic Regression of Disease Severity

Regressors	Adjusted Odds Ratio	Confidence Interval	p-value
Monocyte	0.956	0.782 – 1.170	0.664
Neutrophil	1.206	1.032 – 1.411	0.019*
Lymphocyte	1.174	1.001 – 1.378	0.049*
Intercept	1.75×10^{-07}	3.08×10^{-14} – 0.998	0.050

DISCUSSION

Understanding of the COVID-19 disease and its clinical and laboratory features gives healthcare workers the capacity to be able to effectively manage cases and provide patient care. Studies regarding COVID-19 biomarkers are emerging to address the knowledge gaps in its diagnostic utility, assessment of disease severity, and prediction of disease prognosis and infectiousness of the patients.¹⁸ Monitoring changes in Ct values over time could provide information about the progression of the infection and the effectiveness of the immune response or treatments. Ct values could potentially be used to assess the effectiveness of vaccines and treatments. A decrease in viral load (increase in Ct value) after treatment or vaccination might indicate a positive response. The study aims to determine the association of the biomarkers with the Ct values of confirmed COVID-19 patients.

The study was limited to the data available in the medical records section of SLH. Since the researchers are not personally involved in the data collection procedure, measurements may have to be taken at face value, except if it really is outside the expected range of values, and the researchers cannot verify the accuracy of the measurements. Incomplete documentation, including missing charts, information that was unrecoverable or unrecorded were not included in the study. Since the majority of the data came only from admitted patients, association with asymptomatic COVID-19 cases cannot be generalized as they require no hospitalization.

Specimen collection from suspected COVID-19 patients is commonly done through nasopharyngeal swabs (NPS), oropharyngeal swabs (OPS), or both. 70.85% of the specimens tested from confirmed COVID-19 patients admitted in San Lazaro Hospital were obtained through OPS. The concentration of genetic material varies depending on the specimen type, in turn influencing the Ct values. A systematic review revealed that although NPS remains to be the gold standard for specimen collection regarding COVID-19 related concerns, as it is considered the highest-yield sample, other specimens also show promising results.²² Ultimately, the collection procedure, the time between sampling and testing, adequacy and quality of the sample, the presence of inhibitors in the sample, and the PCR test kit and reagents used affect the Ct values, regardless of the specimen type.²³

Table 5 showed the distribution of confirmed COVID-19 patients admitted in San Lazaro Hospital according to disease severity as per DOH classification. Mild disease cases are confirmed COVID-19 patients that present symptoms that include, but are not limited to, fever, cough, sore throat, anosmia, ageusia, myalgia, and anorexia preceding the onset of respiratory symptoms, but without evidence of viral pneumonia or hypoxia. Similarly, confirmed COVID-19 patients with additional comorbidities and/or of 60 years of age or above, with non-severe pneumonia, a respiratory rate (RR) of <30 breaths per minute, and an oxygen saturation (SpO₂) of ≥94% at room air are considered to be moderate COVID-19 cases. Severe cases are presented with pneumonia with either signs of respiratory distress that requires oxygen supplementation, a RR ≥30 breaths per minute, or an SpO₂

Table 14. Results of Correlation Coefficient of N gene Ct values

VAR vs. N Gene	R	R ²	N	p-value
<i>Ferritin</i>	-0.0986	0.01	91	0.35
<i>Procalcitonin</i>	-0.0282	0.0008	138	0.74
<i>Hematocrit</i>	0.0233	0.001	292	0.69
<i>WBC</i>	0.0860	0.0074	290	0.14
<i>Neutrophil</i>	0.0041	0.00002	289	0.94
<i>Lymphocyte</i>	0.0375	0.0014	292	0.52
<i>Monocyte</i>	-0.2176	0.0473	98	0.03
<i>Platelet</i>	0.0208	0.0004	294	0.72
<i>Urea</i>	-0.0054	0.00003	271	0.93
<i>D-dimer</i>	0.0025	0.000006	191	0.97
<i>LDH</i>	-0.0279	0.0008	128	0.75
<i>PT</i>	0.0126	0.0002	188	0.86
<i>PTT</i>	0.0747	0.0056	184	0.31
<i>K</i>	0.0674	0.0045	272	0.27
<i>Na</i>	-0.0892	0.0079	273	0.14
<i>Creatinine</i>	-0.1356	0.0184	277	0.02
<i>SGPT</i>	0.0396	0.0016	262	0.52
<i>SGOT</i>	0.0081	0.00007	264	0.90

Table 15. Results of Correlation Coefficient of ORF gene Ct values

VAR vs. ORF Gene	R	R ²	N	p-value
<i>Ferritin</i>	-0.2552	0.0651	77	0.03
<i>Procalcitonin</i>	-0.0953	0.0091	125	0.29
<i>Hematocrit</i>	0.0506	0.0026	259	0.42
<i>WBC</i>	0.0543	0.0029	260	0.38
<i>Neutrophil</i>	-0.0488	0.0024	258	0.43
<i>Lymphocyte</i>	0.0806	0.0065	261	0.19
<i>Monocyte</i>	-0.1922	0.03696	87	0.07
<i>Platelet</i>	0.0627	0.0039	261	0.31
<i>Urea</i>	-0.0175	0.0003	239	0.79
<i>D-dimer</i>	0.0246	0.0006	172	0.75
<i>LDH</i>	-0.0784	0.0061	112	0.41
<i>PT</i>	0.0530	0.0028	168	0.50
<i>PTT</i>	0.0538	0.0029	164	0.49
<i>K</i>	-0.0269	0.0007	244	0.68
<i>Na</i>	0.0490	0.0024	243	0.45
<i>Creatinine</i>	-0.0981	0.0096	242	0.13
<i>SGPT</i>	0.0373	0.0014	232	0.57
<i>SGOT</i>	0.0261	0.0007	234	0.69

<94% at room air. COVID-19 patients are classified under critical if they are presented with pneumonia with any of the following complications: an impending respiratory failure that requires either non-invasive or invasive ventilation, acute respiratory distress syndrome, sepsis or shock, deteriorating sensorium, multi-organ failure, or thrombosis.²⁴

Only 3.86% of the patients were classified as mild COVID-19 cases, and more than half had severe to critical disease. Despite the high cases of severe to critical disease, it was shown in Table 4 that the mortality in the study is 2.14%, which is lower compared to other tertiary hospitals in the region. As of July 2021, the case fatality rate in the Philippines is 1.75% with NCR, specifically the City of Manila where the San Lazaro Hospital is situated, being one of the top regions with the most number of COVID-19 cases.^{25,26} During that time period, the number of COVID-19 cases has breached the 1.5 million mark as new cases were reported. Multiple variants from other countries have also reached the Philippines such as the more contagious UK-COVID-19 B.1.1.7 variant, South African B.1.351 variant, P.3 variant, and South Asian B.1.617 variant as reported by multiple news outlets and the Department of Health alongside the Philippine Genome Center.^{27,28} The high morbidity and low mortality rate may indicate that the capacity to address public health needs in order to control the disease and handle emergency situations is limited, compared to the hospital's medical care capacity. In combating highly transmissible infections such as the SARS-CoV-2, it has been shown that non-pharmaceutical interventions appear to be more effective and sustainable.²⁹

The study assessed the characteristics of the patients from their clinico-demographic factors and laboratory profiles and its relationship with the Ct values obtained from SARS-CoV-2 Real-Time RT-PCR in San Lazaro Hospital. More than half of the confirmed COVID-19 patients admitted in San Lazaro Hospital were females at 60.52%. Despite having females as the majority in the distribution of confirmed COVID-19 patients in San Lazaro Hospital according to sex, there was no significant difference observed between expired and discharged COVID-19 patients in terms of sex distribution. In relation to that, simple regression analysis showed that sex and disease severity were not significant predictors of clinical outcome. This is in contrast with studies that show that COVID-19 morbidity and mortality is higher in males than females.^{30,31} Although, females are more associated with higher risk of long COVID-19 than males according to the study of Notarte et al.³² To some extent, differences in biological factors such as hormones and immune response, behaviors, lifestyle choices, societal roles between sexes, may influence disease severity and mortality.³³ Understanding of sex as a risk factor can be important in determining which groups are more vulnerable to the disease, therefore public health and clinical interventions can be formulated and implemented accordingly.

In terms of disease severity and clinical outcome, there was also no significant difference observed between expired

and discharged patients and their case severity. Several risk factors may influence COVID-19 disease severity, including the presence of comorbidities, smoking status, complications, and age, among others, as disease severity classification follows a certain criteria as discussed previously. Such complications due to disease severity may cause patient mortality, but it is not a significant predictor of the patient's clinical outcome. Those with severe cases of the disease, especially in the older population, already have an underlying chronic disease present such as diabetes, hypertension, and cardiovascular disease, and often die due to it, and not due to the virus itself.³⁴ Complications that may arise over the course of admission in COVID-19 patients include respiratory distress syndrome, RNAemia, acute cardiac injury, renal failure, multiple organ failure, secondary infection, and shock. As being infected with the COVID-19 virus entails that major organs and organ systems aside from the lungs, such as the heart, liver, kidneys, blood, and immune system, can also be damaged, routine tests that are able to assess and evaluate the state of these organs are requested for patients. This study aims to correlate laboratory findings to potentially be a biomarker for COVID-19 infection.^{35,36}

Table 6 showed the data collected from the patients of the most common routine laboratory tests requested and performed on confirmed COVID-19 patients upon admission in which values may deviate from normal ranges in the presence of the disease. This includes a complete blood count (CBC); measurement of coagulation indicators—prothrombin time (PT), partial thromboplastin time (PTT), and D-dimer; inflammation markers—lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), and procalcitonin (PCT); and biochemical measurements of liver profile—SGPT and SGOT; and kidney profile—urea, creatinine, and electrolytes. In addition to that, nucleic acid tests that target genetic material of the virus, specifically the N gene (nucleocapsid) and ORF gene (open reading frame), were also performed. The N gene and ORF gene is a promising target gene for RT-PCR in the detection of the COVID-19 virus as it is produced in large quantities in infected cells and for their specificity to the virus.³⁷ The study of Zhang et al., also showed that the detection of the N gene is more often in previously positive patients as it tends to have less variation than other genetic material, therefore monitoring of patients can be more efficient and less costly.³⁸ Our study revealed that 5% of the patients have been tested more than twice for the purpose of monitoring. Some patients with a longer duration of hospital admission have even been tested seven times. In a similar setting as the Philippines, it may pose a challenge for the healthcare system as RT-PCR testing can be costly and time consuming. Altogether, these tests were used to assess the status of the patient which is important in triaging, determining the course of treatment, and monitoring throughout the course of hospitalization.³⁹

Logistic regression was utilized in order to analyze the relationship between the pertinent laboratory tests and disease

severity. The patient's hematologic markers, inflammatory biomarkers, coagulation studies, and kidney profile deviates more from the normal range in patients with severe to critical disease. It was found specifically that the patient's white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count, urea, LDH, CRP, and PTT are significant predictors of disease severity. Current studies show that the WBC count, neutrophil count, monocyte count, LDH, CRP, and urea tend to increase more in COVID-19 patients, especially in severe cases, with lymphopenia.^{40,41} From the findings of the multiple logistic regression and forward variable selection, there are statistically significant differences only in the neutrophil and lymphocyte counts with regard to disease severity. It was found that, controlling for other variables, the odds of having severe to critical disease increases by 20.6% (95% CI [1.032 – 1.411]) for every one unit increase in neutrophil count. Similarly, controlling for other variables, the odds of having severe to critical disease increases by 17.4% (95% CI [1.001 – 1.378]) for every one unit increase in lymphocyte count. These laboratory tests, however, were not significant predictors of patient mortality.

The Ct values for both ORF and N genes have also been shown to not be significant predictors of both disease severity and the patient's clinical outcome. This is in line with the study of Cho et al., Le Borgne et al., and Pawar et al. where disease severity and clinical outcome have no significant associations with Ct values.⁴²⁻⁴⁴ Different studies have inconsistent results wherein some studies suggest that viral load appears to be higher in patients with severe disease.⁴⁵⁻⁴⁷ Ct values might also be associated with different viral variants. Some variants could lead to higher viral loads, impacting disease spread and severity. A study by Hasanoglu et al. shows that the Ct values appear to be lower in asymptomatic patients, therefore in non-severe cases.⁴⁸ The timing of testing should be taken into consideration in relation to the onset of symptoms to have a more conclusive result, as it was shown in the study of Shah et al. that the Ct values vary depending on how far along the course of the illness the patient was tested.⁴⁹ As mentioned earlier, in severe to critical COVID-19 cases, patients tend to already have existing comorbidities and the complications that may arise during the course of the infection are most likely to be the cause of patient mortality and disease severity. The aforementioned studies did consistently report the association of viral load with increased transmissibility of the disease. Some studies suggested that patients with lower Ct values (higher viral loads) might experience more severe symptoms and a worse clinical outcome, while those with higher Ct values (lower viral loads) might have milder or asymptomatic cases. However, this is not a strict rule, and other factors like the individual's immune response and pre-existing conditions play a significant role in disease severity.

Results showed that as the monocyte count and creatinine levels decrease, N gene values increase. Similarly for the ORF gene, it was observed that as its value increases, the monocyte count and ferritin levels decrease. An increased monocyte

count is seen in confirmed COVID-19 cases. However, in severe cases, decreased monocyte counts are observed.⁵⁰ This is in line with the study's findings that monocyte counts are significant predictors of disease severity. A decrease in monocyte count results in an increase in Ct values or lower viral load. As viral load is not a significant predictor of disease severity, as shown in our results, we could not conclude that a lower viral load can indicate severe disease. This is in line with most studies, that does not indicate a significant relationship between Ct values or viral load and disease severity.⁵¹ As for creatinine levels, there have been studies linking kidney damage to COVID-19.⁵² The study observed a decrease in creatinine levels in patients with lower viral load. The ACE2 is the primary receptor for the COVID-19 virus, and it has been shown to be expressed in the kidneys, even more than the lungs.⁵² In our results, creatinine levels are not indicative of disease severity. However, renal complications are commonly seen in COVID-19 patients, in which it can be a long-term complication of the disease.⁵³ Lastly, decreased ferritin is observed in increased Ct values, based on the results of correlation analysis. Studies have explored the correlation between ferritin values and COVID-19 disease.^{54,55} The study of Kaushal et al. reported that higher levels of serum ferritin were seen in COVID-19 patients compared to those without the disease. The study of Desai et al. showed that patients presenting with severe to critical disease showed higher ferritin levels compared to mild to moderate severity.⁵² This is in line with the study of Cheng et al. in which they reported that serum ferritin was associated with disease severity, as well as disease prognosis.⁵⁵ Ferritin as a biomarker for COVID-19 can be further explored.

CONCLUSION

With a high morbidity and mortality rate across the world and multiple strains continuously emerging, the novel coronavirus has been a great public health concern ever since it became a global pandemic. Strengthening diagnostics capacity for disease detection, surveillance, treatment and management, and monitoring are vital to ease the burden on healthcare facilities. RT-PCR is the gold standard for diagnosing COVID-19 infections wherein the common nucleic acid targets include the ORF and N genes. The test offers quantitative results through the reporting of the Ct values or the number of amplification cycles it takes to detect a fluorescent signal from the samples in which we can derive the patient's infectivity and viral load. Specimens tested are commonly acquired through NPS or OPS to achieve the highest genetic yield possible. The study showed that the Ct values for both ORF and N gene were not significant predictors of both disease severity and clinical outcome. Multiple studies have shown to have inconsistent results with regard to the association of Ct values, disease severity, and clinical outcome. This may be due to differences in the timing of testing in relation to the onset of symptoms.

Furthermore, the existing comorbidities of the patient and the complications that may arise during the course of infection, may be the cause of patient mortality and progression of disease severity. Laboratory markers for blood, coagulation, inflammation, kidney, and liver function may be altered in COVID-19 cases and they serve as supplemental information for proper management and monitoring of patients. This study stratified the patients according to disease severity from mild, moderate, severe, and critical according to DOH's case severity classification of COVID-19. Despite the majority of the cases being classified as moderate and more than half of the patients having severe to critical disease, the mortality rate in this study is low with only 2.14% of the patients succumbing to death compared to other tertiary hospitals in the region. In terms of differences in sex, there was no significant difference observed between expired and discharged patients, and were not significant predictors of the clinical outcome. However, studies have reported that females tend to be more associated with the risk of having long COVID-19, wherein they experience more long-term symptoms of the disease. This may be attributed to the differences in societal and biological factors between the sexes. In terms of COVID-19 disease severity and mortality, the study showed that although disease severity and complications throughout the patient's hospital admission may cause an untimely expiration of the patient, disease severity is not a significant predictor of the clinical outcome of the patient. Such complications that may arise include respiratory distress syndrome, cardiac injury, organ failure, or a secondary nosocomial infection. As such, it is important to monitor the patient's laboratory biomarkers in order to determine the proper course of treatment and management for each case. The study showed that the patient's WBC count, neutrophil count, lymphocyte count, monocyte count, urea, LDH, CRP, and PTT were able to predict disease severity, but were not significant predictors of the patient's clinical outcome or mortality. The odds of having severe to critical disease increases by 20.6% for every one unit increase in neutrophil count, and 17.4% for every one unit increase in lymphocyte count. On the other hand, results showed that Ct values are not a significant predictor of disease severity. This is consistent with other studies that reported that viral load does not necessarily correlate to the disease prognosis. Comorbidities in patients, especially in severe COVID-19 cases, complications may contribute to poor prognosis. Lastly, our results reported the correlation between laboratory parameters and Ct values. It showed that as the monocyte count, creatinine levels, and serum ferritin values decrease, the viral load also decreases. These biomarkers can be further explored to aid in the monitoring of COVID-19 patients. It is important to note that while there is a general trend in the association between Ct values and clinical outcomes, there is also a lot of variability. Many other factors, including the patient's age, underlying health conditions, immune response, and the stage of infection at which the sample was taken, can influence the relationship.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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23. Annex B: Description of Case Severity Classification of COVID-19 for adult and pediatric patients Table 1. Description of Case Severity Classification of COVID-19 for adult and pediatric patients Case type/severity Description of case type Adult Pediatric: Mild disease with risk factors [Internet]. n.d. [cited 2021 Jun]. https://www.philhealth.gov.ph/circulars/2022/003/AnnexB_CaseSeverityClassificationandDefinitions.pdf
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