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Laboratory features of hospitalised patients with COVID-19 in Jersey, UK

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ABSTRACT

COVID-19 is an acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, more than 550 million cases and 6 million deaths have been reported worldwide. This study investigated the laboratory features in hospitalised patients with COVID-19 and determined risk factors for in-hospital mortality.

This retrospective observational study included laboratory results of confirmed cases of hospitalised patients with SARS-CoV-2 infection in Jersey (UK) between March–December 2020 (subject to inclusion criteria), and a control group. Furthermore, COVID-19 patients were split into two sub-groups, based on outcome (non-survivors vs. survivors). Logistic regression was used to determine risk factors for in-hospital mortality.

A total of 81 COVID-19 cases and 100 controls were included in this study. In the COVID-19 group, 59.3% of subjects were male, and the overall mortality was 33.3%. The main laboratory changes were

the following: 95.1% of patients presented with raised C-reactive protein (p<0.001), 85% showed increased fibrinogen (p<0.001), 70% had prolonged prothrombin time (p=0.014), 51.9% suffered from lymphopenia (p<0.001), 42% had elevated gamma glutamyl transferase (p=0.011) and 35.8% demonstrated raised creatinine concentration (p=0.002). Non-survivors were older than survivors (median age: 82 vs. 74 years, p=0.003) with substantial lymphopenia (p=0.018), high creatinine level (p=0.009), and leukocytosis (p=0.018). Increased in-hospital mortality risk was 6.7-fold in patients presenting with a lymphocyte count <0.85 x10^9/L, 5.3-fold with red blood cell distribution width >14%, 4.9-fold with white cell count >9.5 x10^9/L, and 3.3-fold for those presenting with creatinine >100 µmol/L. Age ≥82 years was significantly associated with death, and male gender a risk factor for hospital admission in COVID-19.

These results demonstrate that routine haematology and biochemistry tests may allow for risk-stratification of hospitalised patients with COVID-19.

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INTRODUCTION

COVID-19 is an acute respiratory infection caused by a new strain of coronavirus first identified in December 2019 in Wuhan - China, initially named 2019-nCoV, and now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1,2). Initial epidemiological investigations suggested a seafood and wet animal wholesale market in Wuhan was associated with the outbreak (3). Current evidence indicates that SARS-CoV-2 has a zoonotic origin, which subsequently evolved resulting in human-to-human transmission (4).

Seven coronavirus species are known to cause human disease: four human coronavirus (HCoV) strains, known as HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU, are capable of infecting the upper respiratory tract, and are responsible for 15–30% of all common cold cases; and three highly pathogenic strains, capable of infecting the lower respiratory tract, causing severe pneumonia: severe acute respiratory syndrome coronavirus (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), and the newly identified SARS-CoV-2 (1,5,6). SARS-CoV-1 was responsible for outbreaks in Guangdong Province - China in 2002 and 2003 (about 8,000 cases worldwide with a case fatality rate of approximately 10%), whereas MERS-CoV caused outbreaks in the Middle East in 2012 (about 2,500 cases reported with an estimated case fatality rate of 36%) (7). SARS-CoV-2 which led to the current outbreak of COVID-19, rapidly spread to eighteen countries outside China between late December 2019 and the end of January 2020, leading the World Health Organisation (WHO) to declare COVID-19 a pandemic on the 11th March 2020 (1). At the time of writing, more than 180 million COVID-19 cases had been reported in 219 countries and territories around the world, with almost 4 million deaths (8). The United Kingdom is one of the worst affected countries, with 4.9 million cases and more than 128 000 deaths reported, whereas China (where the outbreak originated) reported 91 847 cases, and 4 636 deaths between December 2019 and July 2021. In contrast, Jersey (Channel Islands, UK) reported 3 674 cases and 69 deaths, over the same period (8,9). Direct comparisons between countries are challenging due to important variations in the testing and diagnosis criteria used, and the way COVID-19 deaths are recorded in different countries (10).

Studies have shown that up to 42.5% of all cases of SARS-CoV-2 infection may remain completely asymptomatic (11). However, up to 20% of infected individuals may develop severe disease, including acute respiratory distress syndrome (ARDS), pneumonia or pulmonary inflammation

(6). The latter has been associated with novel pulmonary-specific vasculopathy process classified as pulmonary intravascular coagulopathy (12,13). It is thought that SARS-CoV-2 may cause direct pulmonary infection of endothelial cells, via ACE-2 receptors, potentially triggering COVID-19 associated vasculopathy (14). Other mechanisms that may exacerbate endothelial cell damage and organ dysfunction in severe COVID-19 include pro-inflammatory cytokine generation, complement activation and severe hypoxia (15).

A number of recently published studies report potential changes linked to hospitalised patients with COVID-19, particularly lymphopenia, raised D-dimer, lactate dehydrogenase and C-reactive protein (CRP), and low albumin (16-19). In addition, older age has been systematically linked to higher mortality rates in COVID-19 patients (17,20–24). Published studies so far are very heterogeneous and important differences in reported findings exist between different cohorts. Most describe the clinical presentation of hospitalised patients with COVID-19 disease in China and the USA. However, European data is more limited. Analysis of the reported number of cases/deaths, and data from the first European studies revealed important differences in terms of the demographics, laboratory features, and mortality rates in hospitalised patients between countries (24,25), showing published findings cannot simply be extrapolated to individual countries.

The aim of this study is to investigate the main laboratory features of hospitalised patients with COVID-19 disease in Jersey – Channel Islands, UK, and to determine if certain changes on admission results may be associated with disease severity. Additionally, risk factors for in-hospital death in this COVID-19 group were also determined. This study also aims to contribute to the international data on this current topic, addressing the lack of published data on European cohorts of patients.

MATERIAL AND METHODS

Study design and participants

This retrospective observational study was performed at the General Hospital in Jersey (Channel Islands, UK), and approved by the local Research and Ethics Committee (Ref: 2020/HCSREC/03). All laboratory confirmed cases of SARS-Cov2 infection between March – December 2020, in patients admitted to hospital or already hospitalised at the time of testing were considered for inclusion in this study. Documented clinical information was reviewed to establish if COVID-19 was the primary reason for admission, and whether patients were symptomatic and/or required hospital treatment for COVID-19, either on admission or throughout hospitalisation (inclusion criteria). Individual signs and symptoms, and pre-existent comorbidities were excluded from the analysis due to this information not being available for all patients. Asymptomatic patients with laboratory confirmed SARS-Cov2 infection, who did not require COVID-19 treatment (either on admission or throughout their hospital stay), and had been admitted for other primary reasons, where deemed non-COVID-19 admissions, and excluded from this study. Hospital-acquired COVID-19 cases were assumed in light of prolonged hospitalisation with evidence of previous negative SARS-CoV-2 tests and flagged as known contact with other COVID-19 patients or healthcare workers in the hospital. The control group consisted of 100 patients admitted for other reasons, during the same period, had shown at least two negative SARS-CoV-2 tests on admission/during their hospital stay and remained negative until discharged from hospital.

Data collection and laboratory investigations

Patient demographics (age, gender) and laboratory results were extracted from the laboratory information management system (when available): haematology (haemoglobin (Hb), red

blood cell distribution width (RDW), platelets (PLT), white blood cells (WBC), and five-part differential), haemostasis (prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer), and biochemistry (renal profile (urea, creatinine), liver function tests (albumin, total protein (TP), bilirubin (BIL), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), and alanine aminotransferase (ALT)), and CRP). The electronic patient record system was used to inform the level of care received, length of hospital stay, and outcome.

Laboratory confirmation for SARS-CoV-2 was defined as a positive result of real time reverse transcriptase–polymerase chain reaction (RT-PCR) assay using a nasopharyngeal/oropharyngeal swab. Specimens were initially tested at Public Health England, Porton Down (UK), in-house testing commenced in April 2020 using qualitaive Gene Xpert SARS-CoV-2 RT-PCR test kits (Cepheid, California, USA).

Haematology tests were locally performed on venous blood samples collected into a 4-mL BD Vacutainer tube containing K_2 EDTA (0.184 mol/L; BD, Oxford, UK), and analysis performed on Sysmex XN-2000 analysers (Sysmex Corporation, Kobe, Japan), using flow cytometry technology, with the exception of Hb, which was measured by the sodium-lauryl-sulphate (SLS) method.

Haemostasis studies were performed on venous blood samples collected into 2.7 mL BD vacutainer tubes containing 0.109 mol/3.2% tri-sodium citrate (BD, Oxford, UK), spun at 4000 rpm for 4 min prior to analysis. Samples were analysed using the Werfen IL ACL TOP 550 coagulation analyser (Werfen, Bedford, MA, USA), by a photo-optical method for PT, APTT and fibrinogen assays, and a latex immunoassay method for the D-dimer assay.

Biochemistry tests were performed on venous blood sample collected into a 3.5-mL BD Vacutainer SST II gel tube (BD, Oxford, UK), centrifuged at 3500 rpm for 10 min prior to analysis. The tests were analysed using Ortho Vitros 5600 analysers (Ortho-Clinical Diagnostics, NY, USA) by various methods based on MicroSlide technology.

Statistical analysis

Statistical sample size calculation was not performed given that the sample size consisted of all COVID-19 cases admitted to the General Hospital during the study period, with proviso they met the inclusion criteria. All statistical analyses were performed in the IBM SPSS software (version 26). Differences between groups were calculated using the *t* test if data was normally distributed; otherwise, the Mann-Whitney test was used. Standard deviation (SD) and interquartile range (IQR) (IQR1 – 25th percentile; IQR3 – 75th percentile) were chosen to best describe the dispersion of the data for mean and median, respectively. Categorical variables were compared using the X^2 or Fisher exact test, as appropriate. Probability (p) <0.05 was considered significant for all tests. For consistency, a maximum of 3 decimal places were used for p values therefore, values under 0.001 were reported as p<0.001 (e.g., p=0.0004 was reported as p<0.001).

To ascertain if the statistically significant differences of mean/median values between groups/sub-groups were clinically significant, the percentage of patients with abnormal results were calculated for each parameter showing statistically significant changes, by setting the critical value of interest (e.g., PLT <150 x10^9/L) as a categorical variable; then, the X^2 or Fisher exact test was used (as appropriate) to determine if there was a statistically significant difference (p<0.05) in the percentage of patients showing abnormal results between groups. Normal ranges used to facilitate the interpretation of statistical analysis findings throughout the study are specific for the local adult population in Jersey.

Receiver operating characteristic (ROC) curves were calculated for continuous variables showing statistically significant differences between the survivor and non-survivor sub-groups. The area under curve (AUC) and the 95% confidence interval (CI) were determined to establish optimal cut-off points that maximised sensitivity and specificity to predict death by the Youden's index. These cut-offs were used to transform the continuous variables into binary variables, and univariate and multivariate logistic regression models were applied to calculate the estimated odds ratio and the 95% CI. Variables that were statistically associated with mortality in the univariate analysis were included in the multivariate model, using the forward stepwise likelihood ratio method.

RESULTS

A total of 113 COVID-19 hospitalised patients were identified as having had a positive SARS-CoV-2 RT-PCR test on admission or during hospitalisation: 81 patients met the inclusion criteria and were included in the test group (70 were new admissions, 11 were identified as part of the inpatient screening programme - likely hospital acquired cases); 32 patients were found not to meet the inclusion criteria because COVID-19 was not the primary reason for admission, and they remained completely asymptomatic/did not require any COVID-19 treatment on admission/throughout hospitalisation (13 were new admissions, 19 were identified as part of the inpatient screening programme – likely hospital acquired cases).

Patient group with hospitalised patients with COVID-19 vs. control group

There was no statistically significant difference in age and gender distribution between the COVID-19 group (median age: 75 years, overall range: 28-94 years; 59.3% males) and controls (median: 77 years old; overall range: 19-97 years, 54% males) (Table 1). An analysis of the haematology results revealed the test group showed statistically significant lower PLT, WBC, lymphocytes, monocytes, eosinophils, and basophils, compared with controls. Interestingly, platelet count could not be determined in 4 patients (out of 81) due to PLT clumping (5% of all patients). Haemostasis results showed significantly higher PT, fibrinogen, and D-dimer levels in the COVID-19 group. Biochemistry changes consisted of higher levels of creatinine, GGT, ALT, and C-reactive protein, and lower albumin. Analysis of the differences between categorical variables (Table 2) confirmed that the parameters showing abnormal mean/median values (based on the normal range) were associated with a higher percentage of abnormal results. Importantly, changes in WBC, albumin, and ALT were shown not to be clinically significant.

COVID-19 group were split into two sub-groups based on outcome

Non-survivors were found to be significantly older (median age: 82 years; overall range: 50-94 years) than survivors (median: 74 years; overall range: 28-92 years) and presented with higher median WBC, RDW and creatinine levels and lower lymphocyte count on admission (Table 3). The analysis of categorical variables (Table 4) confirmed the clinical significance of all these changes (except for RDW). No statistically significant differences in haemostasis results were found despite prolonged PT, and lower D-dimer levels were seen in non-survivors. In addition, survivors showed a slightly longer albeit non-significant hospital stay compared to non-survivors (median: 12 days, IQR: 6-23 in survivors vs. 11 days; IQR: 7-18 in non-survivors; p=0.343).

ROC analysis and logistic regression analysis

Table 5 shows the optimal cut-off points established using ROC curve analysis, based on modest but statistically significant AUC values that

Table 1 **Demographics & laboratory features – control and COVID-19 groups**

		COVID-19 group		Control group		
Parameter	**Normal range**	***n***	**Median (IQR) or Mean ± SD**	***n***	**Median (IQR) or Mean ± SD**	***p* value**
Age (years)	N/A	81	75 (61 – 83)	100	77 (56 – 86)	0.868*
Gender N (%)	N/A	81	♂ 48 (59.3%) ♀ 33 (40.7%)	100	♂ 54 (54%) ♀ 46 (46%)	0.478†
Hb (g/dL)	♂ 13.0 – 17.0 ♀ 11.0 – 15.0	81	13.03 ± 2.19	100	12.74 ± 2.10	0.370‡
RDW (%)	10.0 – 20.0	81	13.8 (12.9 – 14.7)	100	13.4 (12.6 – 14.6)	0.318*
PLT (10^9/L)	150 – 450	77	214 (156 – 291)	100	272 (212 – 338)	0.001*[a]
WBC (10^9/L)	3.5 – 11.0	81	8.00 (5.90 – 10.90)	100	9.65 (6.93 – 13.35)	0.004*[a]
Neutrophils (10^9/L)	1.8 – 8.0	81	6.14 (4.07 – 9.75)	100	7.29 (4.75 – 10.15)	0.061*
Lymphocytes (10^9/L)	0.8 – 4.0	81	0.74 (0.51 – 1.15)	100	1.40 (1.02 – 1.87)	<0.001*[a]
Monocytes (10^9/L)	0.2 – 1.0	81	0.52 (0.39 – 0.74)	100	0.67 (0.53 – 0.94)	0.001*[a]
Eosinophils (10^9/L)	0.01 – 0.50	81	0.02 (0.00 – 0.07)	100	0.10 (0.04 – 0.20)	<0.001*[a]
Basophils (10^9/L)	0.01 – 0.10	81	0.02 (0.01 – 0.03)	100	0.04 (0.03 – 0.06)	<0.001*[a]
PT (sec)	10 – 13.0	40	13.7 (12.6 – 16.4)	48	12.7 (11.7 – 14.4)	0.007*[a]
APTT (sec)	22.0 – 37.0	40	30.0 ± 3.6	48	31.0 ± 4.9	0.335‡
Fibrinogen (g/L)	1.7 – 4.8	40	6.41 (5.00 – 6.98)	48	4.48 (3.66 – 5.51)	<0.001*[a]
D-dimer (ng/mL)	0 – 250.0	24	336.5 (227.3 – 599.5)	5	170.0 (123.5 – 234.5)	0.008*[a]

Urea (mmol/L)	2.5 – 7.8	81	7.30 (5.55 – 11.35)	100	6.75 (4.50 – 9.25)	0.078*
Creatinine (µmol/L)	♂ 58 – 110 ♀ 46 – 92	81	80.0 (59.5 – 114.5)	100	69.5 (56.0 – 88.0)	0.023*[a]
Albumin (g/L)	35 – 50	81	37.4 ± 5.5	97	40.0 ± 6.1	0.004[‡a]
TP (g/L)	60 – 80	81	68.0 (64.0 – 73.0)	95	71.0 (65.0 – 76.0)	0.067*
BIL (µmol/L)	0 – 21	81	13.0 (10.0 – 18.0)	96	12.5 (8.3 – 19.5)	0.391*
GGT (U/L)	♂ 15 – 73 ♀ 12 – 43	81	44.0 (31.0 – 137.0)	96	32.5 (19.0 – 55.5)	<0.001*[a]
ALP (U/L)	30 – 130	81	79.0 (65.5 – 104.5)	96	81.0 (66.5 – 116.3)	0.517*
ALT (U/L)	♂ 0 – 50 ♀ 0 – 35	79	27.0 (18.0 – 38.0)	95	21.0 (16.0 – 29.0)	0.003*[a]
CRP (mg/L)	0 – 10	81	63.0 (34.0-168.0)	97	14.0 (5.0 – 35.5)	<0.001*[a]

Key: *♂ male; ♀ female;* Mann-Whitney U test; † X^2 test; ‡ t-test; [a] statistically significant (p<0.05).*
Abbreviations: n: total number of patients tested; IQR: Interquartile range (Q1, Q3); SD: Standard deviation; N/A: Not applicable; CRP: C-reactive protein.

Table 2 **Analysis of categorical variables for all parameters showing statistically significant differences – controls and COVID-19 group**

	COVID-19 group		Control group		
Categorical variable	***n***	**N (%)**	***n***	**N (%)**	***p* value**
PLT <150 x10^9/L	77	17 (22.1%)	100	6 (6.0%)	0.002*[a]
WBC >11.0 x10^9/L	81	20 (24.7%)	100	32 (32.0%)	0.280*
Lymphocytes <0.8 x10^9/L	81	42 (51.9%)	100	16 (16.0%)	<0.001*[a]
Monocytes <0.2 x10^9/L	81	4 (4.9%)	100	0 (0.0%)	0.038[†a]
Eosinophils <0.01 x10^9/L	81	25 (30.9%)	100	3 (3.0%)	<0.001*[a]

Basophils <0.01 x10^9/L	81	81 (8.6%)	100	0 (0.0%)	0.003†a
PT ≥13.0 sec	40	28 (70.0%)	48	21 (43.8%)	0.014*a
Fibrinogen >4.8 g/L	40	34 (85.0%)	48	18 (37.5%)	<0.001*a
D-dimer >250.0 ng/mL	24	16 (66.7%)	5	1 (20.0%)	0.130†
Creatinine ♂ >110 µmol/L ♀ >92 µmol/L	81	29 (35.8%)	100	16 (16.0%)	0.002*a
Albumin <35 g/L	81	23 (28.4%)	97	16 (16.5%)	0.056*
GGT ♂ >73 U/L ♀ >43 U/L	81	34 (42.0%)	96	23 (24.0%)	0.011*a
ALT ♂ ≥50 U/L ♀ ≥35 U/L	79	18 (22.8%)	95	16 (16.8%)	0.325*
CRP >10 mg/L	81	77 (95.1%)	97	60 (61.9%)	<0.001*a

Key: *♂ male; ♀ female;* X^2 test; † Fisher exact test; [a] statistically significant (p<0.05).*
Abbreviations: n: total number of patients tested; N: number of patients with abnormal results, based on categorical variable tested; CRP: C-reactive protein.

Table 3 **Demographics & laboratory features – hospitalised patients with COVID-19 based on outcome**

		COVID-19 non-survivors		COVID-19 survivors		
Parameter	**Normal range**	***n***	**Median (IQR) or Mean ± SD**	***n***	**Median (IQR) or Mean ± SD**	***p* value**
Age (years)	N/A	27	82 (74 - 87)	54	74 (57 - 81)	0.003*a
Gender N (%)	N/A	27	♂ 16 (59.3%) ♀ 11 (40.7%)	54	♂ 32 (59.3%) ♀ 22 (40.7%)	1.000†
Hb (g/dL)	♂ 13.0 - 17.0 ♀ 11.0 - 15.0	27	12.42 ± 2.49	54	13.33 ± 1.99	0.080‡
RDW (%)	10.0 - 20.0	27	14.1 (13.0 - 15.3)	54	13.4 (12.6 - 14.4)	0.028*a
PLT (10^9/L)	150 - 450	24	230 (167 - 330)	53	211 (153 - 281)	0.367*
WBC (10^9/L)	3.5 - 11.0	27	9.50 (6.10 - 13.60)	54	7.30 (5.48 - 9.40)	0.042*a

Neutrophils (10^9/L)	1.8 - 8.0	27	7.34 (4.20 - 11.83)	54	5.42 (3.89 - 7.51)	0.085*
Lymphocytes (10^9/L)	0.8 - 4.0	27	0.63 (0.47 - 0.81)	54	0.99 (0.54 - 1.35)	0.025*[a]
Monocytes (10^9/L)	0.2 - 1.0	27	0.58 (0.43 - 1.03)	54	0.52 (0.37 - 0.73)	0.300*
Eosinophils (10^9/L)	0.01 - 0.50	27	0.03 (0.01 - 0.08)	54	0.01 (0.00 - 0.06)	0.125*
Basophils (10^9/L)	0.01 - 0.10	27	0.02 (0.01 - 0.04)	54	0.02 (0.01 - 0.03)	0.058*
PT (sec)	10 - 13.0	12	15.4 (12.4 - 18.8)	28	13.6 (12.7 - 15.6)	0.400*
APTT (sec)	22.0 - 37.0	12	31.7 (27.8 - 33.0)	28	29.1 (27.1 - 30.8)	0.128*
Fibrinogen (g/L)	1.7 – 4.8	12	6.17 ± 2.08	28	6.33 ± 1.74	0.813‡
D-dimer (ng/mL)	0 - 250.0	5	262.0 (231.5 - 676.5)	19	358.0 (215.0 - 620.0)	0.915*
Urea (mmol/L)	2.5 - 7.8	27	7.70 (5.80 - 16.20)	54	6.95 (5.15 - 9.75)	0.092*
Creatinine (µmol/L)	♂ 58 – 110 ♀ 46 – 92	27	103.0 (63.0 - 123.00)	54	76.0 (55.8 - 96.5)	0.024*[a]
Albumin (g/L)	35 - 50	27	36.3 ± 5.1	54	38.0 ± 5.6	0.185‡
TP (g/L)	60 - 80	27	66.6 ± 6.3	54	69.6 ± 7.6	0.077‡
BIL (µmol/L)	0 - 21	27	12.0 (9.0 - 18.0)	54	13.5 (10.0 - 18.0)	0.488*
GGT (U/L)	♂ 15 – 73 ♀ 12 - 43	27	67.0 (31.0 - 160.0)	54	43.0 (30.5 - 93.0)	0.437*
ALP (U/L)	30 - 130	27	80.0 (68.0 - 102.0)	54	78.0 (57.5 - 110.8)	0.408*
ALT (U/L)	♂ 0 - 50 ♀ 0 - 35	26	26.5 (18.0 - 39.0)	53	29.0 (18.0 - 38.0)	0.830*
CRP (mg/L)	0 - 10	27	67.0 (37.0 - 176.0)	54	61.0 (33.8 - 158.3)	0.700*

Key: *♂ male; ♀ female;* Mann-Whitney U test; † X^2 test; ‡ t-test; [a] statistically significant ($p<0.05$).*
Abbreviations: n: total number of patients tested; IQR: Interquartile range (Q1, Q3); SD: Standard deviation; N/A: Not applicable; CRP: C-reactive protein.

Table 4 Analysis of categorical variables for all parameters showing statistically significant differences – hospitalised patients with COVID-19 based on outcome

	COVID-19 non-survivors		COVID-19 survivors		
Categorical variable	***n***	**N (%)**	***n***	**N (%)**	***p* value**
RDW >15 %	27	7 (25.9%)	54	11 (20.4%)	0.571*
WBC >11.0 x10^9/L	27	11 (40.7%)	54	9 (16.7%)	0.018*[a]
Lymphocytes <0.8 x10^9/L	27	19 (70.4%)	54	23 (42.6%)	0.018*[a]
Creatinine ♂ >110 µmol/L ♀ >92 µmol/L	27	15 (55.6%)	54	14 (25.9%)	0.009*[a]

Key: *♂ male; ♀ female;* X^2 test; † Fisher exact test; [a] statistically significant (p<0.05). Abbreviations: n: total number of patients tested; N: number of patients with abnormal results, based on categorical variable tested.*

maximised sensitivity and specificity to predict death. Univariate logistic regression analysis demonstrated that all selected parameters with determined cut-offs were significantly associated with death. Multivariate logistic analysis indicated that RDW >14% (OR = 5.335), WBC >9.5 x10^9/L (OR = 4.855), lymphocyte count <0.85 x10^9/L (OR = 6.694), and creatinine >100 µmol/L (OR = 3.280) (Table 6) were risk factors for death in hospitalised patients with COVID-19.

DISCUSSION

The median age of the hospitalised patients with COVID-19 included in this study was 75

Table 5 ROC curve analysis of selected parameters

Parameter	ROC curve analysis			
	AUC	**95% CI**	***p* value**	**Cut-off selected**
Age (years)	0.707	0.586-0.827	0.003[a]	≥ 82 years
RDW (%)	0.650	0.528-0.772	0.029[a]	> 14 %
WBC (10^9/L)	0.639	0.504-0.775	0.042[a]	> 9.5 x10^9/L
Lymphocytes (10^9/L)	0.653	0.530-0.777	0.025[a]	< 0.85 x10^9/L
Creatinine (µmol/L)	0.654	0.526-0.782	0.024[a]	> 100 µmol/L

Key: *[a] statistically significant (p<0.05 for the AUC = 0.500). Abbreviations: ROC: Receiver operating characteristic; AUC: Area under curve; CI: Confidence interval (CI of AUC).*

Table 6 ROC curve analysis of selected parameters

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age ≥ 82 years	4.210	1.542-11.492	0.005[a]			
RDW >14%	4.156	1.560-11.069	0.004[a]	5.335	1.524-18.674	0.009[a]
WBC >9.5 x10^9/L	3.630	1.330-9.909	0.012[a]	4.855	1.358-17.364	0.015[a]
Lymphocytes <0.85 x10^9/L	4.717	1.642-13.555	0.004[a]	6.694	1.845-24.290	0.004[a]
Creatinine >100 µmol/L	5.091	1.872-13.845	0.001[a]	3.280	1.005-10.699	0.049[a]

Key: *[a] statistically significant (p<0.05). Abbreviations: OR: Odds ratio; CI: confidence interval.*

years, which is comparable to that reported in the UK (median age: 73 years) (21). An overall mortality rate of 33.3% was found, higher than the inpatient mortality reported in China (28%) (17) and Germany (24%) (24). Patients in this study had a higher median age than patients in China (median age between 48-62 years) (17,18,26–30), in the USA (median age between 58-63 years) (22,23,31), and in other European countries (median age between 63-69 years) (20,24,25). Like several other studies, an association was found between older age and increased mortality from COVID-19 (17,21–23), which might partially explain the higher mortality rate seen in this cohort. However, a direct comparison with overall mortality rates reported by other international studies is difficult given that the vast majority included patients who remained in hospital at the time of reporting; e.g., the UK study reported an overall mortality rate of 26%, with 41% survivors, and 34% still in hospital (21). If the number of hospitalised patients were considered the mortality rate would be between 26–38.8%. Factors to help explain the difference in mortality rates reported include important demographic and epidemiological differences between countries/regions, such as the percentage of elderly individuals, ethnicity, prevalence of co-morbidities/risk factors, such as hypertension, diabetes, obesity (21), and distinct healthcare models/resources available in each area.

Males accounted for most deaths in this cohort (16 deaths, 59.3%), although the mortality rate in males and females was undistinguishable (33.3% in both groups). Like other studies, no statistically significant difference was found in gender distribution between survivors and non-survivors (18,31). The cumulative number of COVID-19 cases reported in Jersey (9) showed more women tested positive (46% males vs. 54% females; p<0.001) however, most of the hospitalised patients were males (59.3% males, vs. 40.7% females; p=0.017) suggesting the male gender is a risk factor for hospital admission in COVID-19, which goes towards explaining the higher number of deaths seen in male patients.

This study found hospitalised patients with COVID-19 presented with a statistically significant lower median WBC, lymphocytes, monocytes, eosinophils, and basophils, compared with controls. Of these, the median lymphocyte

count (0.74 x10^9/L) was below the normal range, affecting 51.9% of patients, which was consistent with other studies (18,24). Lymphopenia was significantly more pronounced in non-survivors, affecting 70.4% of patients. Several studies have shown an association between lymphopenia and severe disease and/or death from COVID-19 (17,18,30). It is thought that SARS-CoV-2 may directly infect lymphocytes via ACE-2 receptors on their surface, contributing to their lysis. The cytokine storm seen in SARS-CoV-2 infection, which results in markedly increased levels of interleukins (IL), particularly IL-6, IL-2, IL-7, granulocyte colony stimulating factor (GCSF), and tumour necrosis factor alpha (TNF-α) may also promote lymphocyte apoptosis (33), having been described in three highly pathogenic coronavirus: SARS-CoV-1, MERS-CoV, and SARS-CoV-2 (30).

An analysis of categorical variables, based on clinically significant values, showed that 30.9% of COVID-19 patients presented with eosinopenia. This is consistent with several studies (26,29,30). Basopenia and monocytopenia were observed less frequently, affecting 8.6% and 4.9% of patients, respectively. Qin *et al.* also reported modest changes in these two parameters (30). Recent studies have shown that eosinophils play a key role against viruses and bacteria (not just in parasitic infections/allergic reactions) through synthesis, storage, and release of several cytokines. Eosinophils can act as antigen presenting cells, stimulating the immune capabilities of T lymphocytes, and are also capable of promoting humoral responses by interacting with B lymphocytes (34). This is thought to contribute to the destruction of these cells, together with the increased mobilisation of eosinophils onto the airway and other epithelial tissues affected by SARS-CoV-2 infection (26). Unlike other studies, we found no association between eosinophil levels and the severity of COVID-19 disease (26,29,30). However, WBC did appear to show prognostic potential given that 40.7% of non-survivors presented with leukocytosis, which was consistent with other studies (17,30) suggesting a more pronounced inflammatory response in severe cases.

Thrombocytopenia was identified in 22.1% of hospitalised patients with COVID-19, despite median values being within normal ranges. This is comparable with other studies, although other authors reported slightly lower median PLT values in their cohorts (17,18,25,35). Earlier studies suggested an association between low PLT count and increased risk of severe disease and mortality in COVID-19. however, no evidence-based cut-off has been defined (31,36). This study found no statically significant difference between survivors and non-survivors.

Haemostasis results revealed COVID-19 patients presented with deranged clotting: 85% of patients showed raised fibrinogen, 70% prolonged PT, and 66.7% elevated D-dimer, although the latter was not statistically significant (due to the low number of D-dimer tests performed). These findings are consistent with other studies (37). A comparison of haemostasis results between survivors and non-survivors suggests limited prognostic potential, although the low number of coagulation studies requested on admission (particularly in non-survivors) may have biased the data. Initial studies from China linked the coagulopathy seen in hospitalised patients with COVID-19 to disseminated intravascular coagulation (DIC) (27,37), however DIC was a rare finding in cohorts consisting of a majority of Caucasian patients (12,38), which is consistent with this study. These changes have been attributed to pulmonary intravascular coagulopathy, which is a distinct pathological process (12,13). D-dimer has been widely reported as a potential prognostic factor in COVID-19 (17,27) however, none of the non-survivors included in this study presented a D-dimer result on admission over potential prognostic cut-off values suggested by other studies (17,28). It would be inappropriate

to draw definite conclusions based on such low number of haemostasis tests, particularly for D-dimer.

The most evident biochemical change in hospitalised patients with COVID-19 was raised CRP (abnormal in 95.1% of patients), which is consistent with other studies (12,24,35). Unlike these studies, we found no significant differences between CRP levels in hospitalised patients with COVID-19, based on patient outcome. Raised CRP is an established finding in several types of pneumonia, and several studies have shown increased amounts of proinflammatory cytokines in serum (which will lead to an increase of several inflammatory markers) are associated with pulmonary inflammation and extensive lung damage in SARS-CoV-1, MERS-CoV and SARS-CoV-2 infection (30,39,40). High levels of CRP are suggestive of a developing cytokine storm in COVID-19 patients.

Other significant biochemical findings were higher creatinine levels in hospitalised patients with COVID-19, compared to controls. Despite median creatinine values being within normal ranges, 35.8% of COVID-19 patients presented with raised creatinine levels. This appeared to have prognostic potential, affecting 55.6% of non-survivors, being consistent with other studies (18,23). Wang *et al.* hypothesised that acute kidney injury could arise from direct effects of the virus, hypoxia, and shock (18) . Furthermore, 42% of hospitalised patients with COVID-19 presented with elevated GGT levels. Changes in albumin and ALT did not appear clinically significant despite statistical significance. This appears to suggest only a small proportion of COVID-19 patients in this cohort had clinically significant liver injury, which would be in keeping with findings from a meta-analysis performed by Li et al. (41). However, an association between low serum albumin and increased odds of in-hospital death has been documented by other studies (19). The relatively small number of non-survivors in our cohort make it impossible to draw definite conclusions.

Finally, this study also showed statistically significant differences in RDW between non-survivors and survivors. This was consistent with other studies (31,42,43). The fact that RDW results were largely within normal range, and no significant differences were found when looking at set categorical variables based on critical values, suggests this is not clinically significant. Despite this, RDW shows a clear prognostic potential, as recently demonstrated in a larger local cohort of COVID-19 patients (44). This test has been widely researched as an independent predictor of mortality in critically ill patients with sepsis (45). This suggests RDW may be a generic predictor of mortality, not directly linked to potential pathological changes directly associated with COVID-19, which might explain why we did not find differences between hospitalised patients with COVID-19 and the control group.

Overall, the wide range of changes in laboratory results seen in this study supports multi-organ involvement. Both SARS-CoV-2 direct invasion of different tissues/organs via ACE-2 leading to organ injury, and the hyperinflammatory response seen in severe cases of COVID-19 have been associated with disease progression, ARDS, heart failure, kidney injury, liver damage, and a wide range of neurological disorders (45).

This study found COVID-19 patients presenting with lymphocyte counts below 0.85 $x10^9$/L were 6.7 times more likely to die from the disease. Likewise, the mortality risk was 5.3 times higher in those presenting with an RDW above 14%, 4.9 times higher in patients presenting with WBC greater than 9.5 $x10^9$/L, and 3.3 times higher for those presenting with creatinine levels over 100 µmol/L. Age ≥82 years was significantly associated with death. This is partially in keeping with literature (17,31), even though suggested cut-off ranges vary considerably between studies. It is

important to note most of the studies published so far focused on investigating the association between laboratory results and the severity of COVID-19 disease. However, a few authors have determined the mortality risk associated with certain changes, making direct comparisons to the findings of this study difficult.

The limitations of this study include being undertaken on a single hospital site (findings may not be applicable to other locations); the retrospective study design meant not all laboratory tests were performed on all patients (potential bias due to a small number of test results, particularly D-dimer); patients may have presented to hospital at varying phases of the disease progression (admission results may not necessarily reflect the initial phase of the disease); earlier cases not offered the same treatments (e.g., steroids given pre-admission) which could have influenced the laboratory results on admission; potential inaccuracies when comparing laboratory data with other studies, given most authors did not include details of the laboratory methods used in their studies, whilst some authors clearly used different technology/assays. Additionally, the control group consisted of SARS-CoV-2 negative patients admitted for other reasons instead of healthy controls (potential bias), although the authors feel may make it more relevant to day-to-day practice in an acute hospital setting. The study design enabled the authors to capture all COVID-19 cases over a defined period, and with a definite outcome: discharged (survivor) or mortality, overcoming limitations seen in other studies, where data from patients still hospitalised at the time of reporting (unknown patient outcome) was included, leading to bias (e.g., lower mortality rates). The inclusion criteria in this study involved a careful review of the clinical data for each patient to exclude patients admitted for other reasons, who remained completely asymptomatic (not requiring COVID-19 treatment), which is important given that asymptomatic individuals might need to seek hospital treatment for a variety of medical reasons/emergencies (e.g., trauma) and consequently, present with underlying changes unrelated to COVID-19. The authors believe a different approach would have biased the results further. Some studies in the USA did demonstrate significant differences between COVID-19 patients seen only in the Emergency Department (mostly asymptomatic cases), and those requiring hospitalisation (22,23).

CONCLUSION

This study showed the highest in-hospital mortality risk was associated with a lymphocyte count <0.85 x10^9/L on admission, followed by RDW >14%, WBC >9.5 x10^9/L, and creatinine levels >100 µmol/L. Age ≥82 years was significantly associated with death, and male gender a risk factor for hospital admission in COVID-19. These results demonstrate that routine haematology and biochemistry tests, available in most laboratories, may allow for risk-stratification of hospitalised patients with COVID-19. Larger studies are necessary to confirm these findings.

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Conflict of interest

There are no competing interests to declare among the authors of this work.

Ethical approval

This study was approved by the Government of Jersey Research and Ethics Committee (reference: 2020/HCSREC/03).

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