COVID-19: Haematological changes and associated mortality risk in hospitalised patients

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1. Introduction

COVID-19 is an acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first detected in China (December 2019) but now widespread (reported in 219 countries and territories). At the time of writing, more than 300 million COVID-19 cases, and 4 million deaths had been reported worldwide, with important variations in mortality rates reported in different countries.
The aim of this study was to investigate the main haematological changes in hospitalised patients with COVID-19 in Jersey and determine risk factors for in-hospital death, contributing to international data on this topic.

2. Materials and Methods

This retrospective observational study was performed at the General Hospital in Jersey (Channel Islands, UK). All laboratory confirmed cases of SARS-Cov2 infection between March – December 2020, in hospitalised patients were reviewed for inclusion in this study (inclusion criteria: symptomatic and/or required hospital treatment for COVID-19, either on admission or throughout hospitalisation). Furthermore, COVID-19 patients were split into two sub-groups, based on outcome (non-survivors vs. survivors). The control group consisted of patients admitted for other reasons, during the same period, who showed at least two negative SARS-CoV-2 tests on admission/ during hospital stay and remained negative until discharged.
Statistically significant changes between groups were defined by probability (p) <0.05, using *t*-test, Mann-Whitney, or X^2/Fisher exact test, as appropriate. In order to ascertain if the statistically significant differences were clinically significant, the percentage of patients with abnormal results was calculated for each parameter showing statistically significant changes, by setting the critical value of interest (e.g., PT ≥13 sec) as a categorical variable; then, the X^2 or Fisher exact test were used to determine if there was a statistically significant difference in the percentage of patients showing abnormal results between groups. Normal ranges quoted are specific for the local adult population in Jersey. Logistic regression was used to determine risk factors for in-hospital mortality in hospitalised patients with COVID-19.

3. Results/ Discussion

A total of 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).

3.1. Comparison of results between hospitalised patients with COVID-19 and controls

Analysis of the differences between laboratory features (table 1) and categorical variables (table 2) in the control and test groups confirmed that the parameters showing statistically significant differences between groups, and abnormal mean/ median values (based on normal ranges) were associated with an higher percentage of abnormal results, including 85% of patients in the test group who presented with raised fibrinogen (p<0.001), 70% with prolonged PT (p=0.014), 66.7% with high D-Dimer (p=0.130), and 51.9% with lymphopenia (p<0.001) (all statistically significant except for D-Dimer).
On the other hand, parameters showing normal mean/ median values (based on the normal range) were associated with milder changes in this group, including 30.9% of patients with eosinopenia (p<0.001), 8.6% with basopenia (p=0.003), and 4.9% with monocytopenia (p=0.038). Importantly, changes in WBC, and D-Dimer did not appear to be clinically significant, despite apparent differences between groups. Detailed data is shown in tables 1 and 2 below.

Table 1. Demographics & laboratory features - control and test groups.

Parameter	Normal range	Test Group *n*	Test Group Median (IQR) or Mean ± SD	Control Group *n*	Control Group 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 ‡
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
RDW (%)	10.0 - 20.0	81	13.8 (12.9 - 14.7)	100	13.4 (12.6 - 14.6)	0.318 *
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

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.

Table 2. Analysis of categorical variables for parameters showing statistically significant differences.

Categorical variable	Test Group *n*	Test Group N (%)	Control Group *n*	Control Group 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 †

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.

3.2. Comparison of results between COVID-19 patients based on outcome

The analysis of categorical variables for the sub-groups consisting of hospitalised patients with COVID-19 based on the outcome (non-survivors vs. survivors), revealed the following clinically significant changes: 70.4% of non-survivors presented with lymphopenia (p=0.018) and 40.7% with raised WBC (p=0.018), despite median results being within normal ranges. Changes in RDW did not appear clinically significant.
Detailed data is shown in tables 3 and 4 below.

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

Parameter	Normal range	Non-survivors *n*	Non-survivors Median (IQR) or Mean ± SD	Survivors *n*	Survivors 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 ‡
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
RDW (%)	10.0 - 20.0	27	14.1 (13.0 - 15.3)	54	13.4 (12.6 - 14.4)	0.028 *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 *

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.

Table 4. Analysis of categorical variables for parameters showing statistically significant differences.

Categorical variable	Non-survivors *n*	Non-survivors N (%)	Survivors *n*	Survivors N (%)	*p* value
WBC >11.0 x10^9/L	27	11 (40.7%)	54	9 (16.7%)	0.018 *a
RDW >15 %	27	7 (25.9%)	54	11 (20.4%)	0.571 *
Lymphocytes <0.8 x10^9/L	27	19 (70.4%)	54	23 (42.6%)	0.018 *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.

3.3. Mortality risk

The overall mortality amongst hospitalised patients with COVID-19 disease was 33%, with higher mortality seen in older patients (47.1% mortality in patients ≥80 years old, and 36.4% in 70–79-year-old patients). There was no significant difference in terms of gender distribution across sub-groups (59.3% males in both sub-groups; p=1.000).
The ROC curve and AUC with 95% CI were calculated for each parameter showing statistically significant differences between survivors and non-survivors, in order to establish the optimal cut-off points that maximised sensitivity and specificity to predict death by the Youden's index (data not shown). D-dimer was analysed due to being frequently mentioned in literature as one of the strongest predictors of mortality in hospitalised patients with COVID-19. The optimum critical point was then selected as cut-off for univariate and multivariate analysis (table 5). This analysis revealed that the highest mortality risk was associated with a lymphocyte count <0.85 x10^9/L on admission, followed by RDW >14%, and WBC >9.5 x10^9/L. Age ≥82 years was significantly associated with death.

Table 5. Risk factors associated with death in COVID-19.

Variables	Univariate analysis OR	Univariate analysis 95% CI	Univariate analysis *p* value	Multivariate analysis OR	Multivariate analysis 95% CI	Multivariate analysis *p* value
Age ≥ 82 years	4.210	1.542-11.492	0.005 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
RDW >14%	4.156	1.560-11.069	0.004 ª	5.335	1.524-18.674	0.009 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
D-dimer >500 ng/mL	1.867	0.238-14.647	0.553			

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

4. Conclusion

- Hospitalised patients with COVID-19 presented with deranged haemostasis (including prolonged PT, raised fibrinogen and D-dimer), and marked lymphopenia. Milder changes included eosinopenia and thrombocytopenia..
- This study found that non-survivors were significantly older, presented with a more pronounced lymphopenia than survivors, and frequently showed elevated WBC on admission.
- This is in keeping with other studies, although important differences in reported findings are evident between different cohorts.
- Age ≥82 years was shown to be significantly associated with death. Additionally, this study suggests male gender is a risk factor for hospital admission in COVID-19, which may explain the higher number of deaths in males (mortality rate between males and females was undistinguishable).
- We established that COVID-19 patients presenting with a lymphocyte count <0.85 x10^9/L were 6.7 times more likely to die from the disease, whereas this risk was 4.9 times higher in patients showing WBC >9.5 x10^9/L.
- RDW revealed prognostic potential: we report a 5-fold increased mortality risk in hospitalised patients with COVID-19 presenting with RDW >14%. This is a fairly recent marker being investigated in COVID-19.

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