Original research

Incidence, pattern and severity of abnormal liver blood tests among hospitalised patients with SARS-COV2 (COVID-19) in South Wales

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ABSTRACT

Introduction SARS-CoV-2 (COVID-19) is a novel coronavirus that emerged in Wuhan, China in late 2019 and since become a global pandemic. As such, its clinical behaviour is a subject of much interest. Initial reports suggested a significant proportion of patients have abnormal liver blood tests. Gwent has experienced one of the highest incidences of COVID-19 infection in the UK, which itself has among the highest COVID-19 impacts worldwide.

Method We set out to report the incidence, clinical pattern and severity of liver blood test abnormalities in hospitalised patients with confirmed COVID-19 in our institution over a 3-week period. Data on clinical outcomes such as admission to intensive therapy unit (ITU), hospital discharge and mortality were recorded.

Results 318 hospitalised COVID-19 positive had liver blood tests available for analysis. Ninety-seven patients (31%) had one or more abnormal liver blood tests and were abnormal admission in 64%. Liver tests were predominantly cholestatic (72%) in contrast to other studies to date. Male gender and abnormal liver blood tests were associated with ITU admission.

Conclusions Almost one-third of admissions with COVID-19 have abnormal LBTs which are typically mild and are associated with male gender. Importantly, we have identified that cholestatic patterns dominate but were not clearly associated with ITU admission or death.

Significance of this study

What is already known on this topic

- The novel coronavirus SARS COV2 (COVID-19) is associated with abnormal liver blood tests, especially ALT.
- Reports have linked abnormal liver blood tests to a more severe disease course.

What this study adds

- In this European cohort, cholestatic liver blood test patterns predominate and are independently associated with poorer clinical outcomes which was not the case for ALT elevations.

How might it impact on clinical practice in the foreseeable future

- These data suggest markers of cholestasis should not be overlooked in terms of their association with adverse outcomes.

INTRODUCTION

SARS-Cov2-related disease (COVID-19) emerged as global health emergency soon after the first reported case in December 2019 in Wuhan City, China.[1] WHO declared it as a pandemic on 11 March 2020. To date, globally over 5 million individuals have been affected in 188 countries with this virus and over 300 000 have died as a consequence. Following the pattern observed in China, the pandemic took root in Europe with cases rising exponentially in Europe, initially in Italy and Spain. The UK has since observed a similar pattern to our European neighbours and to date over 250 000 cases have now been confirmed and over 36 000 deaths reported so far in UK, with numbers continuing to rise.[2]

The pattern of COVID-19 disease and its effects on various organ systems have been studied and reported in the worldwide medical literature since the beginning of the outbreak, even before it was declared a pandemic.[3] Although not

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initially felt to be a prominent feature of the illness, abnormalities in liver biochemistry are being increasingly reported as a direct or indirect consequence of the illness and/or its management.[4 5]

Those early and subsequent reports[4–6] suggest that liver blood test (LBT) abnormalities occur frequently (30%–50%), are typically mild and are dominated by elevations in the alanine aminotransferase (ALT) and/or AST.

An understanding of the impact of COVID-19 disease on the liver is important not only for furthering our understanding of the clinical behaviour of this virus but to identify if such an occurrence is associated with adverse clinical outcomes which at the time of this study had not been definitively determined.

The Aneurin Bevan University Health Board in Wales, UK covers a population of over 639 000 and from early on in the outbreak has been one of the worst affected regions in the UK with over 2000 confirmed cases to date and a rate of 446 cases per 100 000.

METHOD

Consecutive adult patients who were admitted to the Aneurin Bevan University Health Board and tested positive for COVID-19 were identified from the 16 March to the 7 April 2020. All positive COVID-19 PCR swabs are centrally recorded and maintained by the health board's infection control team so we were able to identify all hospitalised COVID-19 positive cases during this time period. Patients with chronically abnormal LBTs prior to a diagnosis of COVID-19 were excluded.

Hospitalised patients were chosen for analysis for the impact of COVID-19 on LBTs as the initial testing strategy within our healthcare system was to predominantly test hospitalised patients and outpatients tested rarely had LBTs measured.

The standard LBT panel in our institution includes bilirubin, alkaline phosphatase (ALP), ALT, albumin and total globulin. For the purposes of this study, the laboratory analytes of interest were bilirubin, ALP and ALT. The normal range for bilirubin in our institution is $<20\,\mu$mol/L, ALP <135 U/L and ALT <55 iU/L. The prothrombin time is not a routine part of the LBT panel but is typically requested only when significant liver disease is suspected. The upper limit of normal for the prothrombin time (PT) in our institution is 12 s. Where the PT was measured, these results are also reported. Albumin and total globulin are very non-specific, especially in the context of acute infection and systemic inflammation and so were considered for analysis.

The health boards' electronic record system (Clinical Workstation) was then interrogated to identify patient demographics and which patients had abnormal LBT's, either at admission or during their hospital stay. Only new abnormalities in LBTs were considered, although only five patients had any pre-existing abnormality in LBTs.

If more than one LBT abnormality was present, we recorded the dominant pattern based on the R factor described in relation to drug-induced liver injury (DILI), whereby an R factor of <2 suggests a cholestatic injury, a figure of between 2 and 5 a mixed pattern and >5 representing hepatocellular injury.

We also recorded whether LBTs were present at the time of admission or developed thereafter, in which case, time to development of abnormal LBTs post hospital admission was also recorded. Clinically important outcomes recorded include hospital discharge, admission to the intensive therapy unit (ITU) and patient mortality.

Statistical calculations were performed using SPSS V.23.0 (IBM Corp).

Normality was assessed using the one-sample Kolmogorov-Smirnov goodness of fit test and non-parametric tests were undertaken (Mann-Whitney U test and Kruskal-Wallis tests for ordinal data and X^2 test for nominal data). Where relevant, median values together with the corresponding 95% CIs are reported.

RESULTS

Over the defined study period, 357 individuals tested positive for COVID-19. Of these 39 were already inpatients due to serious comorbidity and were managed expectantly and had no LBTs undertaken. By necessity, these were excluded from further analysis. There were two patients with chronic hepatitis C without cirrhosis, two patients with alcohol-related cirrhosis. Eight patients were on immunosuppression, two post-renal transplant, two patients with Crohn's disease and four with rheumatoid arthritis.

Of the remaining 318 patients, there were 179 men (56%) and 139 women (44%). The median age was 73 with a range of 19–99 years. The age ranges of COVID-19 positive patients and their mortality are displayed in figure 1.

Females were statistically older than males, 76 years (69.7–75.3) vs 73 years (66.5–71.3), $p=0.021$ (Mann-Whitney U test). The median length of stay for competed episodes (discharge or death) was 10 days (range 1–83). At the end of the study period, just 305/318 patients had completed their acute admission episode.

Of the 318 admissions who had LBTs undertaken, 221 individuals had normal liver tests and 97 had at least one abnormality, representing 31% of the total cohort.

Abnormal LBTs were noted to be more common in males (63/179=35%) than females (34/140=24%) $p=0.039$ (X^2 test).

Among patients with abnormal LBTs, 44% had antibiotics prior to their development and none received antivirals. Antibiotics used were amoxicillin in 11 patients, tazocin in 8, doxycycline in 6, clarithromycin and coamoxiclav in 5 each, clotrimoxazole in four and vancomycin and meropenem in three each.

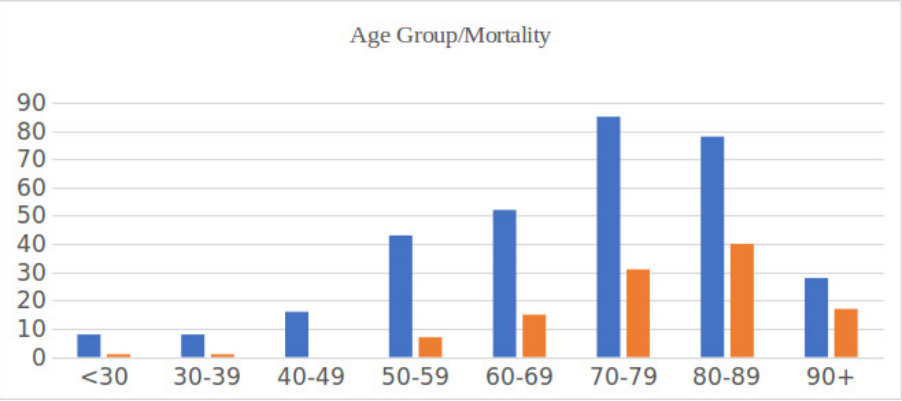

Figure 1 Age ranges of patients admitted with COVID-19 and corresponding mortality.

Unfortunately, the date of antibiotic initiation could not be accurately determined retrospectively.

Patterns of abnormal liver tests

The bilirubin was identified to be abnormal in 42/318 (13%) patients, being an isolated elevation in 11 (26%) with a range of 3–175 μmol/L. Of these 42 patients, 19 (45%) had a normal bilirubin on admission. The ALP was noted to be elevated in 60/318 patients (19%) with a range 49–972, being an isolated elevation in 27 individuals (45%). Of these 60 patients, 36 (60%) had a normal ALP on admission.

An elevated ALT was observed in 59 patients (19%) with a range 8–4476 IU/mL, being isolated in 14 patients (24%). In just six patients was the ALT >5 times the ULN. Among those with an elevated ALT, 32/59 patients (54%) had a normal ALT on admission.

The degree of abnormality in patients with an elevated ALT is represented in figure 2.

The PT was measured in 96 patients (30%) and was found to be abnormal in 29 patients (30% of those measured) who were not already on warfarin. The PT was abnormal in 14/221 pts (6%, range 10–53) with normal LBTs and 15/97 patients (15%, range 10–36 s) with any abnormal LBTs p=0.640 (Mann-Whitney U test).

When the R factor was applied, the patterns of LBTs were as follows: cholestatic in 74%, mixed in 23% and hepatocellular in just 3%.

The relationships between the R factor and gender, age, timing of liver test abnormalities and clinical outcomes are displayed in table 1. There was no significant difference in patterns dependent on whether the patient had abnormal LBTs at admission or developed thereafter. In 10 patients, the R factor changed during the course of admission; from cholestatic to mixed in five patients, from cholestatic to mixed in four and from hepatocellular to mixed in one.

Timing of abnormal LBT

Among the 97 patients with at least one LBT abnormality, 63 were abnormal at admission and in 34 developed as an inpatient, 22 of whom were admitted to ITU. The median interval between admission and abnormal LBTs was 9 days (range 1–18).

Outcomes of COVID-19-related admissions

Serious comorbidities (active respiratory disease, malignancy, cardiac disease, diabetes mellitus, neurological disease, extreme frailty based on performance score 3 or above) were evident in 274 patients with just 44 individuals (14%) having no significant underlying health issues.

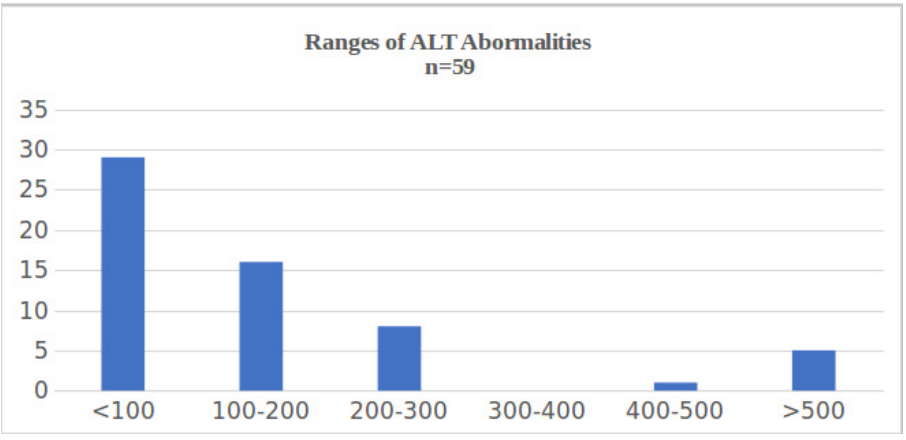

Figure 2 Ranges of ALT abnormalities in COVID-19 positive patients. ALT, alanine aminotransferase.

Table 1 Relationship of pattern of abnormal liver blood tests with demographics, timing of abnormality and clinical outcomes

Pattern based on R factor	Mean age	Male/female	Abn on admission, (%)	Mean LOS	ITU, (%)	Death, (%)
Cholestatic n=72	69	48/24	47 (65)	17	18 (25)	30 (41.7)
Mixed n=21	60	12/9	13 (62)	22	7 (33.3)	5 (23.8)
Hepatocellular n=2	61	1/1	2 (100)	8	0	1 (50)

Abn, abnormal; ITU, intensive therapy unit; LOS, length of stay.

Given COVID-19 has been associated with a profound coagulopathy there remains the potential for portal venous thrombosis (PVT) to be a contributor to abnormal LBTs. Although only 18/97 patients had abdominal imaging (4 with ultrasound, 14 via CT) there was not a single case of PVT identified As of the 23 April 2020, 186 patients had been discharged home or to a rehabilitation facility. In addition, a further 20 patients remain in hospital (13 of whom had abnormal LBTs), comprising patients 15 on ITU and 4 patients who have been discharged from ITU to the wards and 1 patient who was never admitted to ITU.

ITU admissions

LBTs were more commonly abnormal in patients admitted to the ITU 26/38=68% vs 25% of non ITU admissions p<0.001 (X^2 test).

There were 38 ITU admissions (12% of admissions) with a median age of 57 (range 19–78), in comparison to a median age of non ITU admissions of 76, p<0.001 (Mann Whitney U Test). Among ITU admissions, there were more males than female—26 men (median age 57) age and 12 women (median age 55) which trended towards but did not quite reach statistical significance p=0.108 (X^2 test).

Deaths

At the time of analysis, 112 (38% of completed admission episodes, 35% of total cohort) patients have died. The majority of patients who died were of older age with a median age of 79.5 years (95%CI 75.2 to 79.9), compared with a median of 69.5 years (95%CI 64.3 to 69.0) for patients surviving to hospital discharge p<0.001 (Mann-Whitney U test).

Deaths occurred more commonly in men, representing 67% all deaths. Among completed admission episodes, 45% of males died as opposed to 29% of females (p=0.01). Among 21 ITU patients with completed hospital admission episodes, 13 have died of whom 11 (83%) were male (p=<0.001).

Factors associated with pooled poor outcomes (ITU admission/death)

In those with a more severe clinical course (ITU admission or death), male gender (p=0.007), abnormal LBTs on admission p≤0.0001, higher bilirubin (p=0.02) and ALP (p=0.03) were all significantly associated with worse outcome on univariate but not on multivariate analysis.

DISCUSSION

Liver injury has been reported as part of SARS-COV and Middle East respiratory syndrome (MERS) infection in the past. With COVID-19, the GI tract is reported to be one of the most commonly affected organs after the lungs with the liver as a prime target.[7] Different mechanisms of cell injury have been proposed in the literature. It is now known that ACE 2 is a key receptor for viral entry into cells and there is a possibility of a similar mode of hepatocyte injury.[8] However, to date, there is no conclusive evidence supporting this theory. Another suggested mechanism is that viral replication within hepatocytes, just like with other respiratory viruses results in a CD8 +immune response mediated liver injury.[9]

In keeping with the observations of others,[2–7] we have identified that LBTs are indeed common in patients admitted with COVID-19 infection, being present in almost one-third. In contrast to ours study, these other cohorts are characterised by much younger patients and/or a much higher proportion treated with specific antiviral therapies. Akin to other studies, we have also found that LBT, when abnormal, are more commonly so at admission being the case two-thirds of the time.

Application of the R factor (originally proposed in characterising DILI) to characterise the pattern of LBT abnormalities, identifies almost three-quarters of patients as having a cholestatic pattern which is a novel finding. While ITU admission rates were slightly higher in mixed patterns (33% vs 25% p=0.25) and mortality was higher in those with cholestatic injury (42% vs 24% p=0.22) neither of these findings reached statistical significance.

This observation is in contrast to other studies that have suggested that liver injury is predominantly due to an elevation in ALT or aspartate aminotransferase (AST) and that rises in ALP and bilirubin are relatively rare[10–12]

The exception to this relate to a report from Cai *et al*[13] which identified a cholestatic pattern 29%, mixed type and hepatocellular in 21%. This cohort is, however, very different to ours in that median age

was much younger (47 vs 73), over 75% had abnormal LBTs and 84% were treated with lopinavir/ritonavir in contrast to none in our study.

Interestingly a published response to the Cai study identified an elevated ALP and bilirubin in 9.5% and 10%, respectively, and linked an elevated ALP (but not ALT) with deterioration.[14] We also found a significant association of ALP with composite deterioration (ITU admission and/or death) on univariate but not multivariate analysis.

The finding of a cholestatic predominant abnormality is, perhaps, not surprising given that ACE 2 receptors while found in the liver are only minimally expressed on hepatocytes[15] and a recent report has suggested virus binding to ACE 2 positive cholangiocytes but not hepatocytes.[16]

Male gender has already been established as a risk factor for poorer outcomes in COVID-19. The UK Intensive Care National Audit and Research Centre reports[17] that 70% of ITU admissions are male and males have an ITU mortality of 53% vs 38% for females. Our own experience shows a lower proportion of males (56%) among ITU admissions but a much higher mortality among men representing with 11 of the 13 ITU deaths. Furthermore, although males made up just over half of admissions they accounted for two thirds of with LBTs, ITU admissions and deaths. We also demonstrate that male gender is associated with a greater likelihood of abnormal LBT.

While abnormal LBTs were more common in the ITU population the picture this may be due to the consequences of multiorgan dysfunction rather than COVID-19 per se as all 22 of the 38 patients admitted to ITU who had abnormal LBTs only developed them after admission, with a median time to development of 8 days (range 2–20 days).

Among patients who develop abnormal LBTs after admission (particularly those admitted to ITU), sepsis, ischaemia, antibiotic therapy and systemic inflammation can all contribute to a bystander type of liver injury and a cholestatic pattern of injury. There remains no direct evidence of direct viral injury to the liver in injury and, given the blood test abnormalities seem to be generally mild, no convincing evidence that mortality is driven by liver disease or injury.

The strength of this study is that it represents a single centre experience (and one of the few from a European population), allowing capture of all hospitalised patients with COVID-19 19 infection and follow-up from admission to discharge or death. We also characterise, for the first time, a cholestatic predominant pattern.

The major drawback with this study is that it is impossible to be certain that any abnormal LBTs are related to COVID-19 infection. Unfortunately, it has not been possible to establish which patients had profound shock as a potential contributor to LBT abnormalities although ischaemic hepatitis is typically only seen when there is underlying significant right heart dysfunction rather than from hypotension per se and the majority of patients had minimal ALT elevations. In regards other potential cases for liver injury, although almost half 44% of those with abnormal LBTs had antibiotics prior to their development the incidence of abnormal liver bloods is considerably higher than we would expect to see from any of these antibiotic agents. In addition, COVID-19-specific therapies were not used at all in our cohort with the exception of one patient who received hydroxychloroquine as part of a clinical trial.

CONCLUSIONS

We report a high incidence of abnormal LBTs in patients admitted with COVID-19 with the majority being present at the time of admission. Abnormal LBTs are typically mild, and significantly associated with male gender. Importantly, we have identified that cholestatic patterns dominate and are associated but are not clearly associated with increased mortality.

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Contributors AY developed the idea for the project, collected data and wrote the manuscript. DRM collected data and wrote, reviewed and helped edit the manuscript. SAAG collected data and assisted with writing the manuscript. HNH assisted with statistical analysis and helped write and edit the manuscript. MIY collected data and helped edit the manuscript. FY collected data, assisted in writing and editing the manuscript. MAC collected data and assisted in writing and editing the manuscript.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplementary information. All data were held on Health Board computers on secure drives and each file was password protected. Data were anonymised.

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