The impact of SARS-CoV-2 B.1.1.7 on circulating biomarkers in hospitalised patients during the second wave of the COVID-19 pandemic in the UK

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1. Background

- Mutations in SARS-CoV-2 variants have the potential to circumvent immune control, allowing evasion from immunity induced by vaccines or natural infection[1]
- The impact of SARS-CoV-2 variants on clinical outcomes also remains a serious concern, where mutations in key proteins may cause more severe disease characteristics[2]
- The B.1.1.7 variant, associated with a 40%–80% increase in transmissibility, rapidly became the dominant strain in the UK from late 2020[3]
- This variant accrued 23 mutations across the genome including mutations affecting the receptor binding domain conformational change in the spike protein[4]
- This period was characterised by increased hospitalisation, disease severity and death rates and there remains uncertainty as to whether this variant exhibits increased pathogenicity[5,6]

2. Methods

- 1160 positive samples selected from those received for clinical diagnostics or screening purposes between October 2020 and April 2021
- Cumulative levels of blood biomarkers associated with severe COVID-19 disease[7] were examined from laboratory-confirmed symptomatic inpatients
- Measurements taken from the second wave (Dec 2020-April 2021) and the period immediately preceding (Oct-Nov 2020)
- Biomarker values were logged and compared between groups using the independent t-test
- A small cohort (n=83) from December 2020 - April 2021 sequenced through NGS, or obtained from a time period when B.1.1.7 VOC was not in circulation within the region
- Patient metadata including sample date, age, sex, admission to hospital and mortality, as well as clinical parameters including laboratory data and patient outcomes were made available
- Where available, matched B.1.1.7 status and biochemistry parameters were compared using modified z-scores to explore any differences associated to B.1.1.7 status

3. Results

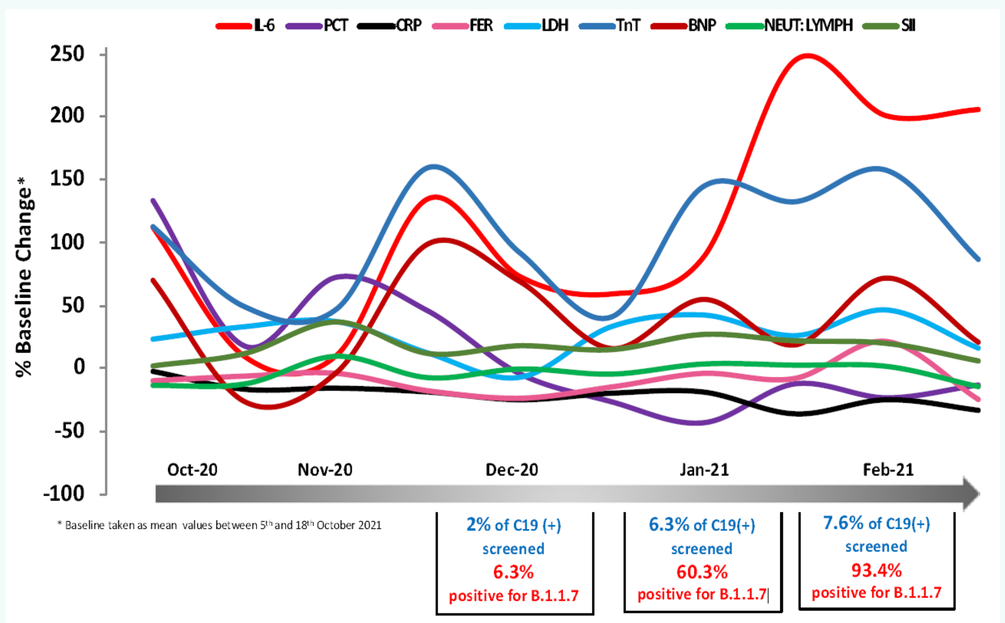

Fig 1. Percentage change across two weekly time intervals for biomarkers included in the COVID panel. Comparison baseline values taken as the first two weeks in October

- Temporal trajectories of biomarkers highlighted an unexpected 2.5-4 fold rise in IL-6 post-January 2021 (fig 1). This was specific for IL-6 and it remained elevated through the decline of cases comprising the second wave

Table 1. Median values for COVID biomarkers for two time points related to the appearance of the B.117 variant in the regional population

	PCT (ug/L)	IL-6 (ng/L)	CRP (mg/L)	FER (ug/L)	LDH (U/L)	TNT (ng/L)	HB (g/L)	Neut: Lymph	SII
Oct 5th - Jan 10th	1.8	129	88	1095	679	38	123	10.7	2905
Jan 11th - April 18th	1.1	233	76	1191	719	50	121	11.1	3027

- A significant difference was noted between groups for both IL-6 (P=<0.01) and CRP (P=<0.01) (table 1)

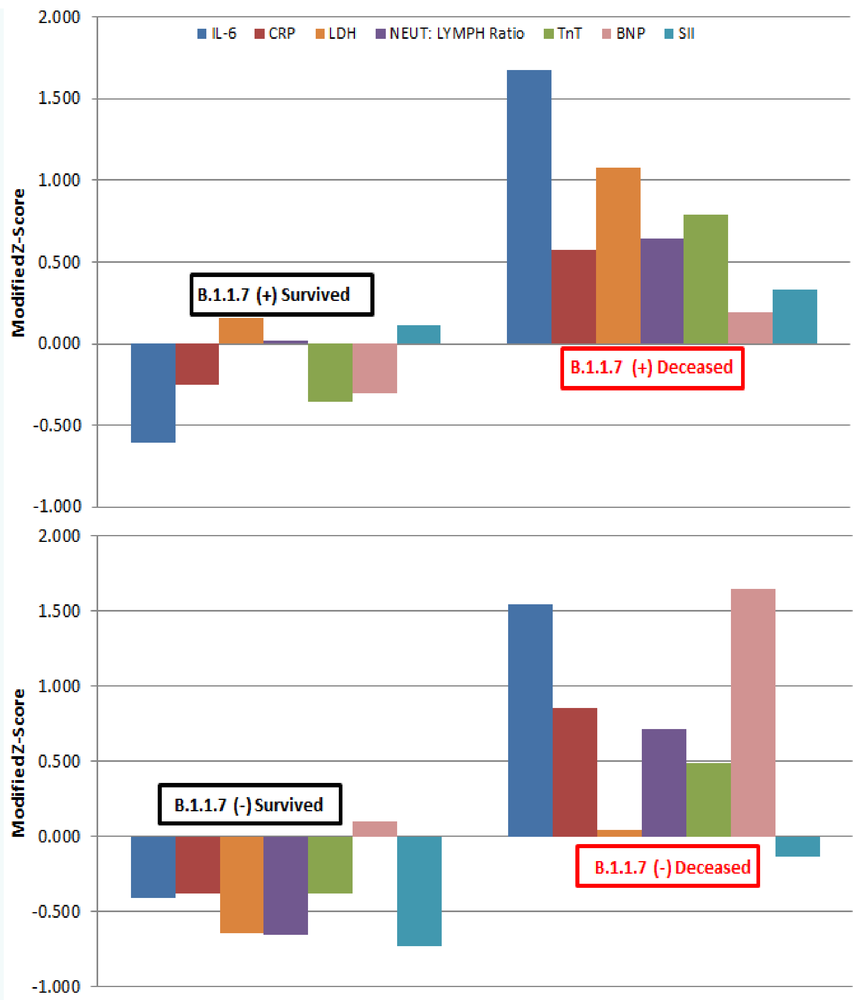

Fig 2. Modified Z scores standardising difference in median values between groups. Values compared across outcome and variant group

- Modified z-scores (fig. 2) showed marked differences and increased levels of inflammatory signals and indices of neutrophilia and lymphopenia between deceased patients and those who survived, which appeared to be independent of virus strain
- Deceased patients infected with B.1.1.7 exhibited exaggerated IL-6 differences compared to survivors, contrasting with moderate changes in biomarkers in the non-variant group

4. Conclusions and Further Work

- Findings suggest a more severe disease phenotype associated with IL-6 induced hyperinflammation is likely to be responsible for the enhanced pathogenesis and severe disease associated with B.1.1.7 variant infection
- Data supports previous proposal that IL-6 may be the best biomarker to indicate excessive inflammation and disease severity[8]
- These data also highlight the importance of continued virus genomic surveillance to monitor new variants, especially those associated with more severe disease phenotypes leading to poor acute and long-term outcomes
- Firm conclusions about a direct causative link between B.1.1.7 VOC and disease severity require availability of detailed clinical data and potential confounders

Further work:

- Gather additional parameter data to allow utilisation of validated severity index tools to compare cohorts
- Multivariate analysis of data to remove co-founders

5. References

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