Poor SARS-CoV-2 spike protein antibody vaccine responses are predictive of severe infections in cancer patients: A national COVID cancer cross-sectional evaluation (UKCCP)

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Running Title: Utility of COVS antibody testing for breakthrough infection and hospitalisation.

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Key points

Question Following COVID-19 vaccination, is the risk of a breakthrough SARS-CoV-2 infection or hospitalisation correlated with spike protein antibody vaccine responses (COVS) in cancer patients?

Findings: In this national COVID-19 cancer cross-sectional survey, an undetectable SARS-CoV-2 antibody response was associated with a significantly increased risk of breakthrough SARS-CoV-2 infection and hospitalisation compared to those that had a positive response. Additionally, antibody titres were significantly lower in cancer patients compared to the general population, with lowest levels observed amongst those with blood cancers.

Meaning: SARS-CoV-2 antibody testing provides a good indication of increased risk from infection or hospitalisation in cancer patients.

Abstract

Importance Accurate identification of patient groups with the lowest level of protection following COVID-19 vaccination is important to better target resources and interventions to the most vulnerable. It is not known whether SARS-CoV-2 antibody testing has clinical utility for high risk groups, such as those with cancer.

Objective To identify if spike protein antibody vaccine response (COVS) following COVID-19 vaccination is associated with the risk of SARS-CoV-2 breakthrough infection or hospitalisation in cancer patients.

Design, Setting and Participants This is a population-based cross-sectional study of cancer patients from the United Kingdom as part of our National COVID Cancer Antibody Survey. Adults with a known or reported cancer diagnosis and had completed their primary SARS-CoV-2 vaccination schedule were included. This analysis ran from the 1st September 2021 to the 4th of March 2022, a period covering the expansion of the UK's third dose vaccination booster programme.

Intervention Roche Elecsys® Anti-SARS-CoV-2 COV-S antibody test

Main Outcomes and Measures SARS-CoV-2 breakthrough infection and COVID-19 hospitalisation.

Results The evaluation compromised 4,249 antibody tests from cancer patients and 294,230 tests from the general population. Patients with cancer were more likely to have undetectable anti-S antibody responses than the general population (4.7% vs 0.1%, $p<0.0001$). Blood cancer patients with leukaemia and lymphoma had the lowest antibody titres. Following multivariable correction, patients with cancer who had an undetectable antibody response were at much greater risk of SARS-CoV-2 breakthrough infection (OR 3.05, 95% CI: 1.96-4.72, $p<0.0001$) and SARS-CoV-2 hospitalisation (OR 6.48, 3.31-12.67, $p<0.0001$) than those that had a positive antibody response.

Conclusion and Relevance COVS antibody testing allows the identification of cancer patients who have the lowest level of antibody derived protection from COVID-19. This study supports larger evaluations of SARS-CoV-2 antibody testing. Prevention of SARS-CoV-2 transmission to cancer patients should be prioritised in order to minimise impact on cancer treatments and maximise quality of life for those with cancer during the ongoing pandemic.

Introduction

The SARS-CoV-2 pandemic remains a healthcare issue despite increasing population immunity from COVID-19 vaccinations and previous infection. Levels of immunity and protection from SARS-CoV-2 differs in the population and some groups are at disproportionate risk. Immunocompromised individuals, such as those with cancer, have a reduced ability to fight infections and there is robust evidence of poor immunological responses to COVID-19 vaccines and boosters. [1 2 3 4 5 6 7 8 9]

There is an unmet need to accurately identify groups with the lowest levels of protection from SARS-CoV-2 infection or severe COVID-19, particularly considering the issue of waning immunity following vaccination. [10] These groups would gain benefit from tailored interventions, such as early treatment programmes or pre-exposure prophylaxis strategies. It remains unclear whether clinical factors alone (demographic, diagnoses and treatments) are sufficient for identification, or whether there is a further role for diagnostic tests such as antibody testing. SARS-CoV-2 antibody testing gives a quantitative assessment of antibodies to either anti-N or anti-S (COVS) antibodies. Anti-N presence denotes the presence of antibodies against the SARS-CoV-2 nucleocapsid protein and is suggestive of previous infection. Anti-S presence denotes antibodies generated against the spike protein and is suggestive of previous infection and/or response to vaccination. To date, no studies have demonstrated that antibody responses following vaccination are predictive of future SARS-CoV-2 breakthrough infections or hospitalisation events in at-risk groups. [11]

This National COVID Cancer Antibody Survey is the largest SARS-CoV-2 antibody study in a cancer cohort, utilising the COVS antibody test. We describe how antibody responses are associated with patient demographics, time since booster and cancer subtype. Additionally, we have performed the first evaluation of antibody testing as a predictor of future SARS-CoV-2 infection and hospitalisation.

Methods

Study Setting

The UK Coronavirus Cancer Programme (UKCCP) is part of the United Kingdom's COVID-19 cancer pandemic response to safeguard, evaluate and protect patients with cancer, (www.ukcovidcancerprogramme.org). This project was a cross-sectional population-based study of antibody responses in cancer patients and covers the period from the 1st September 2021 to 4th March 2022. It was run as part of our National COVID Cancer Antibody Survey (https://covidcancersurvey.uk).

Study Design and Population

The cancer cohort comprises individuals contained within Public Health England's rapid registration national cancer dataset (between 1st January 2018 and 30th April 2021), and who had SARS-CoV-2 antibody tests from the pillar 3 antibody dataset. [12] During the study period, antibody testing was also made available to essential workers, including education, healthcare and social care staff, which formed the population control (unless individuals were contained within the national cancer dataset). During the evaluation period, cancer patients could request an antibody test at any point following vaccination as part of this cross-sectional study. The only study inclusion criteria was completion of their primary vaccination course (i.e. received at least 2 doses; Supplementary Figure 1). Individuals who were on anticoagulants were excluded due to an increased risk of bleeding during home sampling. SARS-CoV-2 antibody sampling was performed using capillary blood sampling as part of the United Kingdom Health Security Agency (UKHSA) Home Antibody Testing Service. Sample analysis was performed centrally at accredited laboratories using the Roche Elecsys® Anti-SARS-CoV-2 S test. The assay that provides quantification of SARS-CoV-2 spike protein antibodies with a saturation value of 25,000 U/ml. All individuals received their antibody test response results in a "positive, negative, void" format. A manufacturer-specified negative result was issued if the result was less than 0.8 U/ml and this was referred to as an undetectable antibody response in this manuscript.

The study was designed as a public health surveillance analysis to support rapid clinical decision making in accordance with the UK Policy Framework for Health and Social Care Research. The study was supported by the Department of Health and Social Care (DHSC), UK Health Security Agency (UKHSA), University of Oxford, University of Southampton, University of Birmingham and Blood Cancer UK with ethical approval from the Public Health England Research Ethics and Governance of Public Health Practice group (PHE REGG NR0278). The funders had no formal role in data analysis, interpretation or decision to submit for publication.

Statistical Analysis

The co-primary outcomes of the study were i) antibody response and titres ii) breakthrough infection and iii) SARS-CoV-2 hospitalisation. Comparisons for antibody responses were made between the cancer cohort and the control population cohort, and within the cancer cohort by cancer subtype. Breakthrough infection and hospitalisation rates were compared within the cancer cohort by level of antibody response.

Antibody testing results were linked to vaccination records from the National Immunisation Management Service (NIMS) and linked to hospital records from the Secondary Use Statistics (SUS) datasets. All linkages required exact matching of NHS numbers. Breakthrough infection was defined as positive SARS-CoV-2 polymerase chain reaction (PCR) test following vaccination. SARS-CoV-2 hospitalisation was defined as a hospitalisation episode between 1 day prior to 14 days following a positive PCR test. Tests with missing data points required for an analysis were excluded from that particular analysis. Pre-defined cancer subgroups included a cancer subtype classification according to the International Classification of Diseases, 10th Revision, using groups specified in our previous analyses and by recorded cancer treatments. [13]

Logistic regression analyses were performed to identify risk of a SARS-CoV-2 breakthrough infection or hospitalisation, based on antibody responses. Multivariable adjustments were performed for pre-defined clinically significant risk factors including age (in deciles), sex, ethnicity and levels of deprivation (IMD). Sensitivity analyses were performed by vaccination dose and cancer subtype. Frequency and cross tabulation of variables was performed with two-sided Fisher's exact to compare categorical data and a Mann-Whitney U test to compare antibody titres.

Results

Overall Description

The cancer cohort consisted of 4,249 antibody tests from cancer patients from between 1st September 2021 to 4th of March 2022. 2,313 of these tests were performed following a second vaccination dose, and 1,936 tests were from tests performed following a third vaccination dose. In this cohort, no patients had more than three vaccination doses. The population control consisted of 294,230 tests of which 230,417 were performed following a second vaccination dose and 63,813 following a third vaccination booster dose. The baseline characteristics of the cancer cohort and population control are displayed in Table 1.

	Cancer Cohort			Population Control		
	Dose 2	Dose 3	Overall	Dose 2	Dose 3	Overall
Overall						
Total	2313	1936	4249	230417	63813	294230
Age						
18-19	0 (0.00)	0 (0.00)	0 (0.00)	849 (0.37)	153 (0.24)	1002 (0.34)
20-29	29 (1.25)	27 (1.39)	56 (1.32)	12184 (5.29)	3941 (6.18)	16125 (5.48)
30-39	99 (4.28)	105 (5.42)	204 (4.80)	35649 (15.47)	9703 (15.21)	45352 (15.41)
40-49	349 (15.09)	273 (14.10)	622 (14.64)	75411 (32.73)	15252 (23.90)	90663 (30.81)
50-59	704 (30.44)	493 (25.46)	1197 (28.17)	61095 (26.51)	16465 (25.80)	77560 (26.36)
60-69	720 (31.13)	586 (30.27)	1306 (30.74)	32976 (14.31)	11703 (18.34)	44679 (15.19)
70-79	378 (16.34)	387 (19.99)	765 (18.00)	11308 (4.91)	5796 (9.08)	17104 (5.81)
80-89	34 (1.47)	65 (3.36)	99 (2.33)	901 (0.39)	772 (1.21)	1673 (0.57)
90+	0 (0.00)	0 (0.00)	0 (0.00)	44 (0.02)	28 (0.04)	72 (0.02)
Sex						
Male	879 (38.00)	740 (38.22)	1619 (38.10)	91068 (39.52)	23050 (36.12)	114118 (38.79)
Female	1434 (62.00)	1196 (61.78)	2630 (61.90)	139348 (60.48)	40763 (63.88)	180111 (61.21)
Ethnicity						
White/ White British	2225 (96.20)	1866 (96.38)	4091 (96.28)	216343 (93.89)	59287 (92.91)	275630 (93.68)
Asian/ Asian British	45 (1.95)	35 (1.81)	80 (1.88)	8140 (3.53)	2642 (4.14)	10782 (3.66)
Black/ Black British	21 (0.91)	9 (0.46)	30 (0.71)	1617 (0.70)	596 (0.93)	2213 (0.75)
Mixed/ Other Ethnic Group	21 (0.91)	25 (1.29)	46 (1.08)	4039 (1.75)	1198 (1.88)	5237 (1.78)
Deprivation, IMD group						
IMD Low (1-3)	462 (19.97)	275 (14.20)	737 (17.35)	40501 (17.58)	12165 (19.06)	52666 (17.90)
IMD Medium (4-7)	904 (39.08)	799 (41.27)	1703 (40.08)	94355 (40.95)	26414 (41.39)	120769 (41.05)
IMD High (8-10)	947 (40.94)	862 (44.52)	1809 (42.57)	95505 (41.45)	25222 (39.52)	120727 (41.03)

Table 1: Baseline characteristics table of cancer cohort and population control.

Following their vaccination course, undetectable antibody responses were identified in 4.7% (199/4249) tests from the cancer cohort. In the population control, significantly fewer individuals had undetectable antibody responses (0.1%, 376/294,230 $p<0.0001$) (Supplementary Table 1). For both the cancer cohort and population control, individuals who had received a third dose booster had significantly higher antibody titres than those who had only two vaccination doses ($p<0.0001$ for both cancer cohort and population control) (Supplementary table 2).

Subgroup analyses identified that undetectable antibody responses were observed in 19.2% (105/546) of blood cancer (haematological) patients and in 4.2% (118/2791) of patients with solid organ malignancies Blood cancer patients had significantly lower antibody titres than solid organ malignancy patients (1872.5 U/ml vs 16,165.0 U/ml, $p<0.0001$). Individuals with a diagnosis of leukaemia and lymphoma had the highest rates of undetectable antibody responses and the lowest antibody titres (Figure 1, Supplementary Table 3).

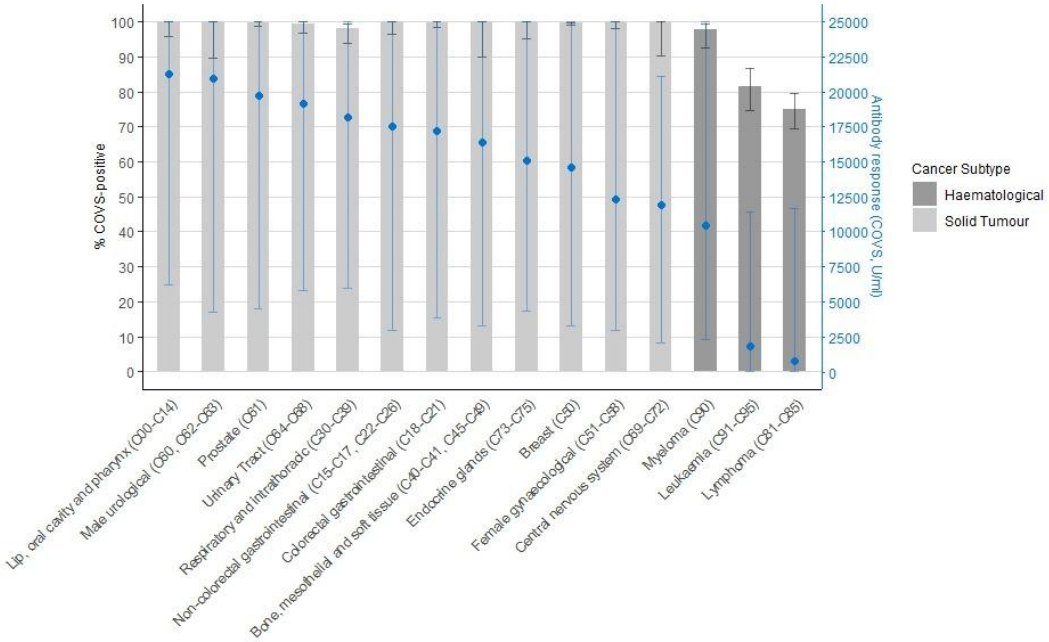

Figure 1. Median SARS-CoV-2 antibody titres and responses in cancer patients based on cancer subtype. Blue dots represent COVS antibody titres (U/ml). Blue error bars denote interquartile range. Black errors bars denote 95% confidence intervals.

We identified that individuals who were recorded as having had systemic anti-cancer therapies (SACT) had lower median antibody titres than those who did not receive SACT (8,131.0 U/ml vs 15,443.0 U/ml, p<0.0001). A difference in antibody titre was not observed for those who were recorded as having had radiotherapy compared to those who did not (supplementary figure 2).

In the cancer cohort, 259 patients went on to have a breakthrough SARS-CoV-2 infection and 55 patients had a SARS-CoV-2 hospitalisation following their antibody test. There were no deaths recorded in the cancer cohort. Cancer patients with a breakthrough SARS-CoV-2 infection had significantly lower median antibody titres than those who did not (2,699.0 U/ml, IQR: 346.9-12,552.0 vs 10,961.0 U/ml, IQR: 1611.0-25,000.0, p<0.0001) (figure 3). Similarly, cancer patients with a SARS-CoV-2 hospitalisation had significantly lower median antibody titres than those who did not (147.0 U/ml, IQR: 6.6-2104.0 vs 10,961.0 U/ml, IQR: 1,611.0-25,000.0, p<0.0001) (figure 2).

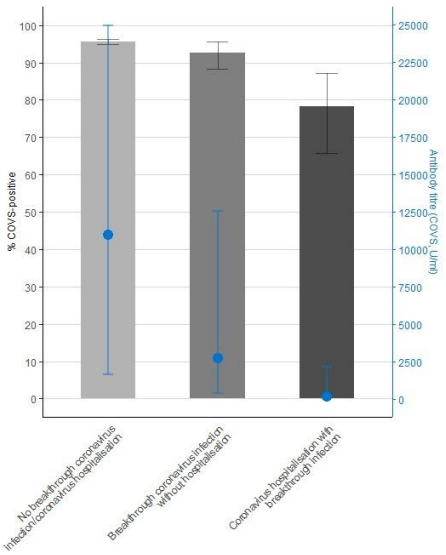

Figure 2. Median antibody titres and % COVS-positive responses in cancer patients in patients who experienced breakthrough infections and hospitalisations. Bars represent % COVS-positive responses. Blue dots represent median antibody titres. Blue error bars denote interquartile range. Black errors bars denote 95% confidence intervals.

Individuals who had an undetectable antibody response were at much higher risk for SARS-CoV-2 breakthrough infection (OR 2.56, 95% CI: 1.69-4.00, 13.57% (27/199) v 5.73% (232/4050), p<0.0001) and SARS-CoV-2 hospitalisation (OR 5.88, 3.13-11.11, 6.03% (12/199) v 1.06% (43/4050), p<0.0001)

than those who had a positive antibody response. This increased risk was still observed when a multiple variable adjusted model was fitted (adjusting for age, sex, ethnicity and levels of deprivation), indicating that antibody responses remained an independent risk factor (breakthrough infection adjOR 3.05, 95% CI: 1.96-4.72, p<0.0001, SARS-CoV-2 hospitalisation adjOR 6.48, 3.31-12.67, p<0.0001). Sensitivity analyses confirmed that this effect was observed irrespective of whether a third dose had been received and whether the individual had a blood cancer or solid cancer diagnosis (Supplementary Table 4)

In order to understand the nature of the relationship between SARS-CoV-2 antibody titre and risk of breakthrough infection and hospitalisation, a logistic regression model was fitted (Figure 3). We observed that the risk of SARS-CoV-2 breakthrough infection and hospitalisation increases as the antibody titre falls below 5,000 U/ml. Comparing those with a titre below 5,000 U/ml, the odds ratio was 3.05 (95% CI: 2.33-4.01, 10.08% (167/1,656) v 3.55% (92/2,594), p<0.0001) for SARS-CoV-2 breakthrough infection and 7.22 for SARS-CoV-2 hospitalisation (95% CI: 3.57-16.10, 2.72% (45/1,656) v 0.39% (10/2,594), p<0.0001), relative to those with a titre above 5,000 U/ml. The relationship between breakthrough and coronavirus hospitalisation and median antibody titres for each cancer subtype is shown in figure 4.

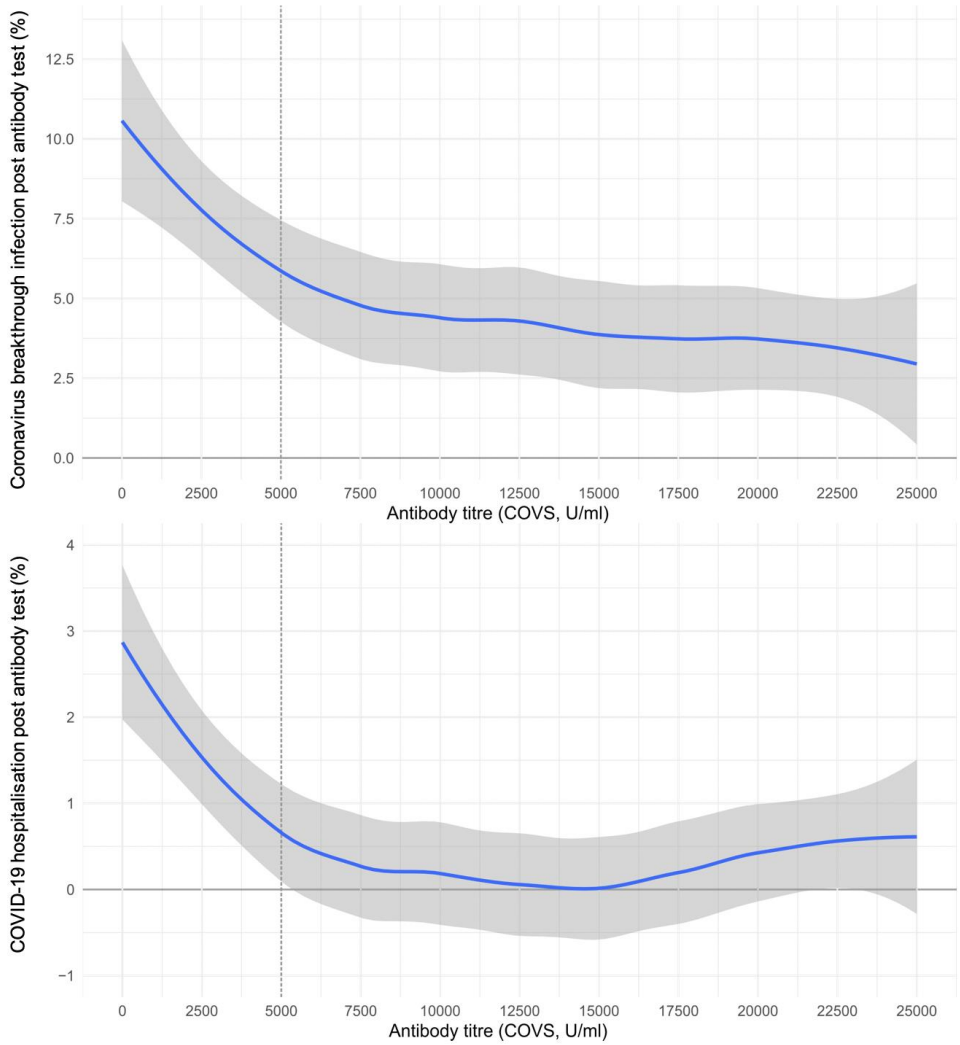

Figure 3- Logistic regression curves demonstrating the relationship between antibody titre and risk of SARS-CoV-2 breakthrough infection (top) and SARS-CoV-2 hospitalisation (bottom). Grey area represents 95% confidence interval. The dotted line is the cut-off at 5,000 U/ml where odds ratios were performed.

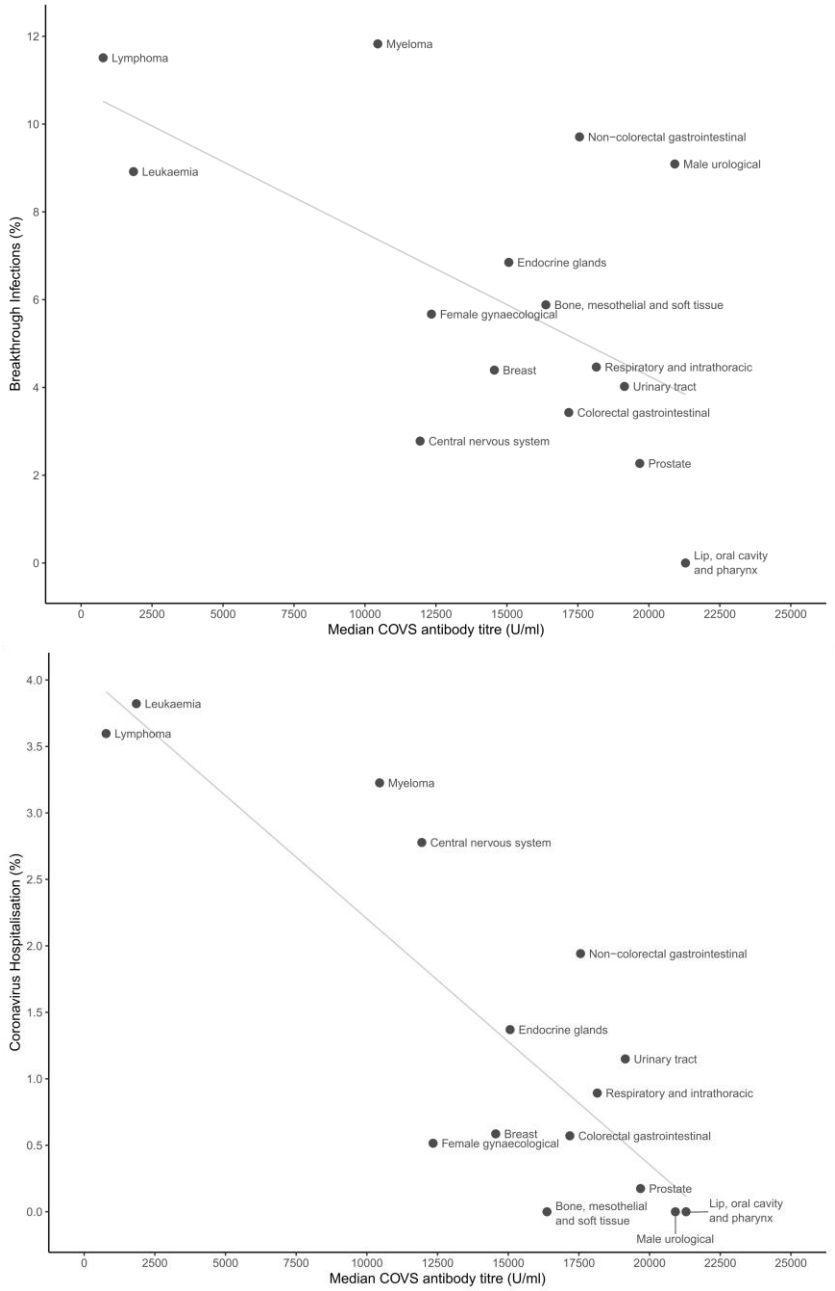

Figure 4- Scatter plot showing the relationship between median antibody titre (U/ml) and breakthrough infections (top panel) and hospitalisation (bottom panel), by cancer subtype.

Discussions

Our National COVID Cancer Antibody Survey is the first study to demonstrate that COVS antibody testing is an effective tool to identify individuals with cancer who have the lowest levels of protection from vaccination. The survey was performed at the end of the United Kingdom's delta variant wave (B.1.617.1) and start of the omicron variant wave (B.1.1.529) and we observed that antibody titres and responses are negatively correlated with risk of breakthrough SARS-CoV-2 infection and hospitalisation. Additionally, we provide confirmation of the heterogenous benefits of vaccination. Low SARS-CoV-2 antibody titres following vaccination are frequently observed from individuals with leukaemia and lymphoma. Low levels of antibody titres may also be observed in other tumour types though at a much lower incidence.

In most countries SARS-CoV-2 antibody testing is not widely available. There are concerns about measuring humoral immunity alone without a measure of cellular immunity by T-cells. Antibody titres are expected to decline over time, even in healthy individuals, and protection against re-infection comes from a combination of circulating antibodies, T cells and memory B cells, which can rapidly produce antibodies following re-exposure. Emerging data shows that cellular immunity is well established after vaccination and infection, even in vulnerable groups, and the large and rapid increase in antibody titres following a second vaccine dose strongly supports the presence of a good memory B cell response. [14] [15] [16]

This survey suggests wider access to antibody testing for individuals with cancer should be evaluated. First, it could inform national guidance for clinicians advising patients, and will provide a risk surveillance strategy that can be used to guide vaccination booster programmes. This is important as the risk of severe outcomes of SARS-CoV-2 infection is heterogenous in different patient groups and changes with SARS-CoV-2 variants, time, availability of effective SARS-CoV-2 treatments and vaccination status/doses. Secondly, it will enable individuals to make better informed choices about personal precautions to reduce the risk of transmission when community SARS-CoV-2 prevalence is high. Finally, healthcare systems will have access to a diagnostic tool to reliably target new interventions, such as early treatment or pre-exposure prophylactic monoclonal antibodies, to those at the highest risk of hospitalisation and breakthrough infections.

There are some potential limitations with this study. The most notable was the cross-sectional nature of our study, capturing a range of intervals after vaccination. Cross-sectional periodic testing however may offer operational benefits compared to a patient-specific testing schedule. Our study is directly applicable and a useful pilot to a healthcare periodic testing model. Additionally, when analysing a specific cancer subtype, numbers of participants are small and it is difficult to draw firm conclusions. Furthermore, it should be acknowledged that the timing of vaccination relative to immunosuppression is likely to be important in determining the level of antibody response and this needs further evaluation. Finally, our survey may be influenced by selection bias, with those concerned about SARS-CoV-2 more likely to participate. We do not envisage that this would alter the relationship between antibody testing and the clinical outcomes of infection or hospitalisation, as patients were informed of their results. Participants who received a negative result would, if anything, be expected to reduce their own risk of infection.

In summary, our National COVID Cancer Antibody Study has demonstrated that COVS antibody testing can identify cancer patients with the lowest level of antibody-derived protection and immunity from SARS-CoV-2 and COVID-19. Prevention of SARS-CoV-2 infection of cancer patients should be prioritised in order to minimise impact on their cancer treatments. Antibody testing could empower these individuals to take additional measures to reduce their risk of infection. Further expansion of antibody testing, to prioritise measures such as pre-exposure prophylaxis, vaccination boosters and early-treatment programmes will help mitigate the direct impact to this group, and also mitigate the indirect impact arising from delays to effective cancer care. In combination, these measures will maximise prognosis and quality of life for those with cancer during the ongoing pandemic.

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