Very low COVID mortality and hospitalization rates in CLL and MBL with repeated vaccination to maximum antibody response

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Introduction

Patients with chronic lymphocytic leukemia (CLL) and monoclonal B-lymphocytosis (MBL) have impaired immunity and high risk of severe COVID infection, hospitalization, and death. The current dominant Omicron variants XBB are now resistant to the prophylactic monoclonal antibodies tixagevimab and cilgavimab (T+C). Hence vaccination, and anti-viral therapy, are the only remaining measures against severe infection. Australia had very low COVID infection numbers from January 2020 until December 2021 when border closures and quarantine measures were removed, by which time community vaccination rates exceeded 95%. For CLL and MBL patients with impaired vaccine responses, we adopted an approach of measuring anti-spike antibody (Ab) response following multiple COVID vaccine doses to achieve the optimum individual response, which significantly increased seroconversion and anti-spike Ab levels (Shen, BJH 2022; Shen, Blood 2022) (Figure 1). We evaluated the effectiveness of this multiple vaccination strategy against severe COVID infection in CLL and MBL patients.

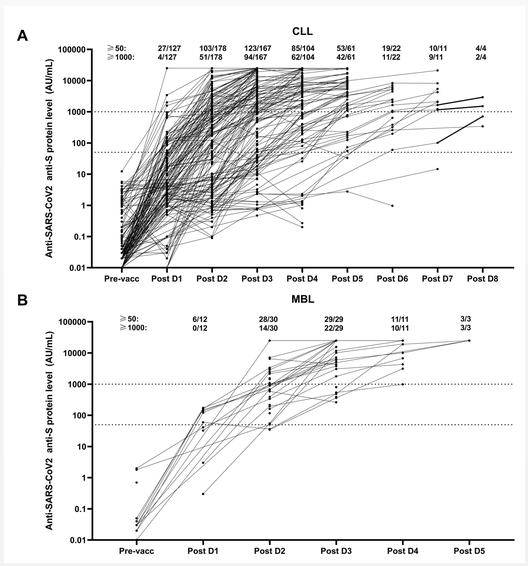

Figure 1. Sequential post vaccination anti-spike protein IgG levels in CLL (A) and MBL (B) patients.

An anti-spike level >50AU/mL is classified as positive response and an anti-spike level ≥1000AU/mL is classified as strong positive response. Red bars in panel C indicate the median anti-spike levels in each group. An anti-spike level of 0 could not be displayed in this figure.

(cited from Shen, Blood 2022)

Methods

Medical and COVID history was assessed in routine consultations, questionnaire and medical records from January 2020 to April 2023 at Royal North Shore Hospital, and Sydney Adventist Hospital, Sydney, Australia with informed consent. Anti-SARS-CoV-2 spike antibody (quantitative) and anti-nucleocapsid (NC) antibody (qualitative) levels were measured as previously reported (Abbott Diagnostics). Vaccination commenced in March 2020, and the first CLL patient developed COVID infection in December 2021.

Very low COVID mortality and hospitalization rate in patients with repeated vaccination

	Total	*CLL*	*MBL*
Number of patients	296	241	55
Age (min-max)	74 (23-95)	74 (23-95)	75 (50-94)
Male	164 (55.4%)	138 (57.3%)	27 (47.3%)
Number of infected (n, %)	151 (51.0%)	129 (53.9%)	22 (40.0%)
Age (min-max)	72 (38-92)	71 (38-92)	73.5 (54-86)
Infected male	87 (57.6%)	77 (59.7%)	10 (45.5%)
Hospitalisation	8 (5.3%)	8 (6.2%)	0 (0%)
Death	1 (0.7%)	1 (0.8%)	0 (0%)
Type of treatment for COVID	Total (151)	CLL (129)	MBL (22)
None	76 (50.3%)	61 (47.3%)	15 (68.2%)
Symptoms relief only	7 (4.6%)	7 (5.4%)	0 (0%)
Anti-viral	68 (45.0%)	61 (47.3%)	7 (31.8%)
▪ **Nirmatrelvir + ritonavir**	37 (54.4%)	33 (54.1%)	4 (57.1%)
▪ **Molnupiravir**	26 (38.2%)	23 (37.7%)	3 (43.9%)
▪ **Remdesivir**	5 (7.4%)	5 (8.2%)	0 (0%)
Duration of COVID *	Total (70)	CLL (59)	MBL (11)
<3 days	4 (5.7%)	2 (3.4%)	2 (18.2%)
3-7 days	28 (40.0%)	23 (39.0%)	5 (45.5%)
7-14 days	21 (30.0%)	18 (30.5%)	3 (27.3%)
>14 days	17 (24.3%)	16 (27.1%)	2 (18.2%)
Anti-NC levels post COVID **	Total (57)	CLL (48)	MBL (9)
Detectable within 2 months	17 (29.8%)	12 (25.0%)	5 (55.6%)
Followed >6 months	Total (19)	CLL (14)	MBL (5)
Detectable after 6 months	10 (17.5%)	9 (18.8%)	1 (11.1%)

**Only included data where detailed questionnaire feedback from patients was received (70 patients)*

***Only included data where anti-nucleocapsid antibody level was measured (57 patients).*

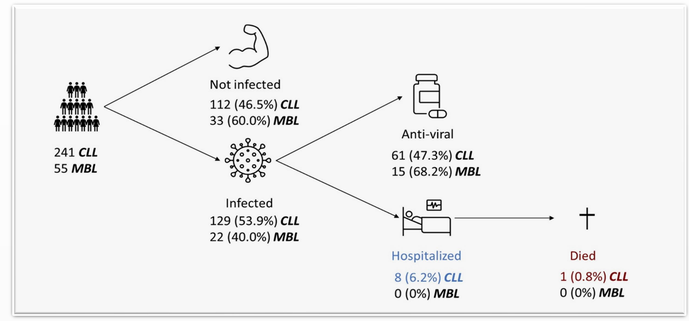

Figure 2. COVID infection and hospitalization rates and patient demographics.

COVID infection rates were **53.9% (129/241) in CLL** and **40.0% (22/55) in MBL patients**. These rates of infection are significantly lower than the incidence of infection in the general Australian community (>90%), and those aged >65 years (>70%).

Hospitalization was required in 8 (of 129) **CLL patients (6.2%) with 1 death (0.8%)**. The duration of admission ranged from 3 to 8 weeks; none required ventilation or ICU admission. Three were on active CLL treatment (2 ibrutinib, 1 venetoclax), but did not correlate to higher risk of hospitalization. There was **1 COVID-related death (1/129, 0.8%)** due to acute anuric renal failure at 4 weeks (with concurrently diagnosed refractory metastatic melanoma). No MBL patient was hospitalized or died.

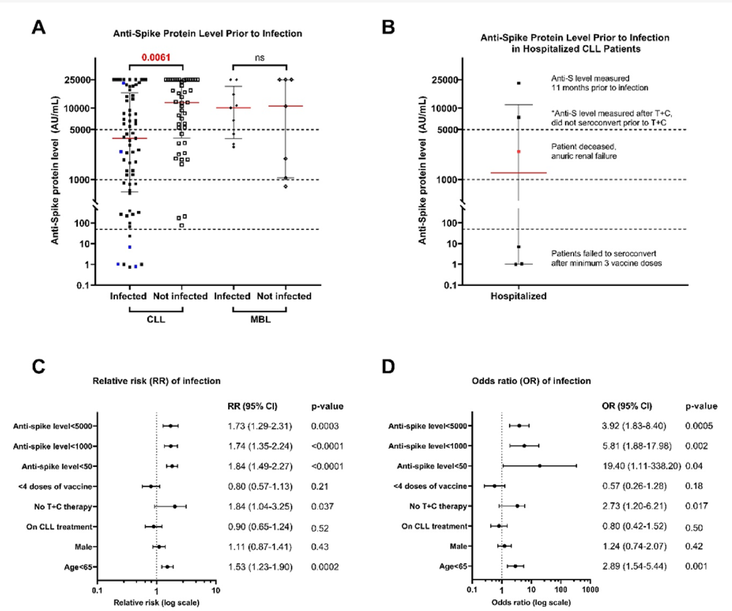

Figure 3. Anti-spike protein levels and factors correlated to COVID infection.

Positive anti-spike levels (>50AU/mL) were documented in **90.6% CLL** (106/117) and **100% MBL patients** (20/20). The median anti-spike levels in CLL patients who developed **COVID infection (3778.8 AU/mL)** were significantly lower compared to those who, to date, have **not (13486.8 AU/mL)** (p=0.0061) **(A,B)**. In MBL, there was no difference in anti-spike levels. CLL patients with low anti-spike levels and younger patients had a higher risk COVID infection **(C,D)**. The number of vaccine doses (median 4), current/active CLL treatment, and gender did not affect risk of COVID infection (Shen, BJH 2023).

The **prophylactic monoclonal antibody combination T+C** was administered to a total of 57 CLL and 1 MBL patients, but 33 already had prior COVID infection. Despite only 9 patients being administered T+C prior to COVID infection, these had **a lower risk of infection (C,D)**. One of these 9 required hospitalization due to COVID 5 months post-T+C **(B)**.

Conclusions

1. **It is important to identify CLL patients who may benefit from additional vaccine doses, as attaining adequate anti-spike levels (≥5000AU/mL) results in very low mortality and hospitalization rates and appears to be the predominant protective factor.**
2. **The small proportion of patients unable to generate an endogenous response rely primarily on anti-viral therapy to mitigate severity.**

References

1. Shen, Y., et al., Br J Haematol, 2022. 197(1):41-51. doi: 10.1111/bjh.18014.
2. Shen, Y., et al., Blood, 2022. 140(25):2709-2721. doi: 10.1182/blood.2022017814.
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The authors have no conflicts of interest to declare.