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Monoclonal B-Cell Lymphocytosis: The Silent Clone the Haematologists Should Not Neglect

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ABSTRACT

Monoclonal B-cell lymphocytosis (MBL) is a hematologic condition defined by the presence of a small clonal B-cell population in the peripheral blood, without clinical or laboratory evidence of lymphoproliferative disorders. It is classified into low-count (LC-MBL) and high-count (HC-MBL) subtypes based on clonal size. HC-MBL shares genetic and biological features with early-stage chronic lymphocytic leukemia (CLL), has a well-established 1%–2% annual risk of progression, and is associated with an increased risk of infections, second malignancies and a reduced response to vaccines due to immune dysfunction. LC-MBL, on the other hand, is a distinct entity with a lower likelihood of progression, but its potential impact on immune function remains unclear. While some studies suggest an association with increased infection risk and immune alterations, further research is needed to clarify its clinical significance. Beyond the risk of progression, MBL is increasingly recognized as a condition requiring careful management due to its broader implications on immune function and cancer susceptibility. Given these risks, preventive strategies are essential for all individuals with MBL, including adherence to cancer screening programs, vaccinations, smoking cessation, sun protection, and a healthy lifestyle to mitigate potential complications.

1 | Introduction—Definition

Monoclonal B-cell lymphocytosis (MBL) is a hematologic condition characterized by the presence of a small clonal B-cell population in the peripheral blood, identified through cytofluorimetric analysis, without any clinical or laboratory evidence of an overt lymphoproliferative disorder or autoimmune disease [1–6]. Since its initial recognition, MBL has gained increasing attention due to its potential as a precursor state to chronic lymphocytic leukemia (CLL) and other B-cell malignancies, and its impact on immune function.

MBL was first described as an asymptomatic clonal B-cell expansion in healthy individuals and was subsequently incorporated into the classification of hematologic disorders by the World Health Organization (WHO). The most recent revised WHO classification 2022 acknowledges MBL as a distinct entity and further refines its categorization based on clone size and immunophenotypic characteristics [7]. According to WHO 2022, MBL is classified into three major subtypes:

1. Low-count MBL (LC-MBL): Defined by a clone size of $< 0.5 \times 10^9$/L, typically with a CLL/SLL-like immunophenotype (CD5+, CD19+, CD20dim).
2. CLL/SLL-type MBL: Previously referred to as high-count MBL (HC-MBL), this form is characterized by a clonal B-cell count of 0.5–5 $\times 10^9$/L and, by definition, a CLL/SLL-

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like phenotype. HC-MBL is distinguished from CLL by an absolute B-cell count of fewer than 5×10^9/L.

3. Non-CLL/SLL-type MBL: This category encompasses monoclonal B-cell expansions that do not exhibit the typical CLL/SLL immunophenotype (CD20+, CD5neg). Instead, these cases often show markers associated with marginal zone B-cell lineage and may have different clinical implications [8].

Despite the updated WHO classification, the International Consensus Classification (ICC) 2022 continues to follow the previous WHO 2018 scheme and previous definitions, categorizing MBL into: (1) CLL-type (low and high count), (2) Non-CLL-type, (3) Atypical CLL-type, based on the presence of the absence of CD5 expression, at different levels [3, 9].

2 | Epidemiology of MBL: Prevalence, Risk of Progression, and Impact on Survival

Since the early 2000s, several epidemiological studies have assessed the prevalence of MBL in healthy individuals, demonstrating that - depending on the sensitivity of detection methods - it can be detected in 3%–17% of the general adult population, increasing with age to over 20% in individuals older than 70 years (Figure 1) [6, 8, 10–12]. Recently, in a landmark study by Slager et al., which analyzed 10,139 individuals aged 40 and older, the overall prevalence of MBL was 17%, with the vast majority (95%) classified as LC-MBL and the remaining 5% as HC-MBL [10]. The study showed a prevalence of MBL among males and confirmed a strong age-related increase in prevalence, from 4% in individuals aged 40%–49% to 42% in those aged 90 and older confirming what previously reported by Nieto et al. and Scarfò et al. [12–15]

MBL is well-established as a precursor to CLL, but its progression risk varies depending on the clonal B-cell count, though some biologic features—such as IGHV mutational status, IGHV gene usage, "CLL-related" cytogenetic aberrations, and mutations in CLL putative driver genes—likely play a role [10, 16–19].

The annual progression rate to CLL requiring treatment is estimated at 1%–2% for HC-MBL, whereas LC-MBL exhibits a much lower risk of progression, if any [10, 16, 20]. In Slager et al.'s study, individuals with HC-MBL exhibited a 74-fold increased risk of developing a lymphoid malignancy compared to controls, while LC-MBL was associated with a 4.3-fold increased risk, highlighting a clear stratification in progression risk. These findings reinforce prior reports that suggest HC-MBL shares more genetic and biologic similarities with early-stage CLL, whereas LC-MBL may represent a more indolent, being potentially an immunologically distinct entity associated to immunosenescence [12, 21]. Supporting this concept, Fazi et al. conducted a prospective population-based study in Val Borbera in Northern Italy, in which 76 individuals with LC-MBL were re-evaluated after a median follow-up of 34 months [16]. They observed that 90% of clones persisted over time, but none progressed to overt leukemia, despite a high prevalence (almost 50%) of CLL-related cytogenetic abnormalities—mostly monoallelic or biallelic 13q deletions—. These observations provided further evidence that LC-MBL may be a stable, non-progressive condition, and that such genetic lesions may occur early in clonal development, without necessarily implying malignant transformation.

However, the impact of LC-MBL on survival remains a subject of debate [10, 16]. Slager et al. found no significant difference in overall survival (OS) between LC-MBL individuals and non-MBL controls, suggesting that LC-MBL is largely a benign condition with minimal impact on life expectancy [10]. In contrast, Criado et al., which prospectively followed 65 LC-MBL individuals over a

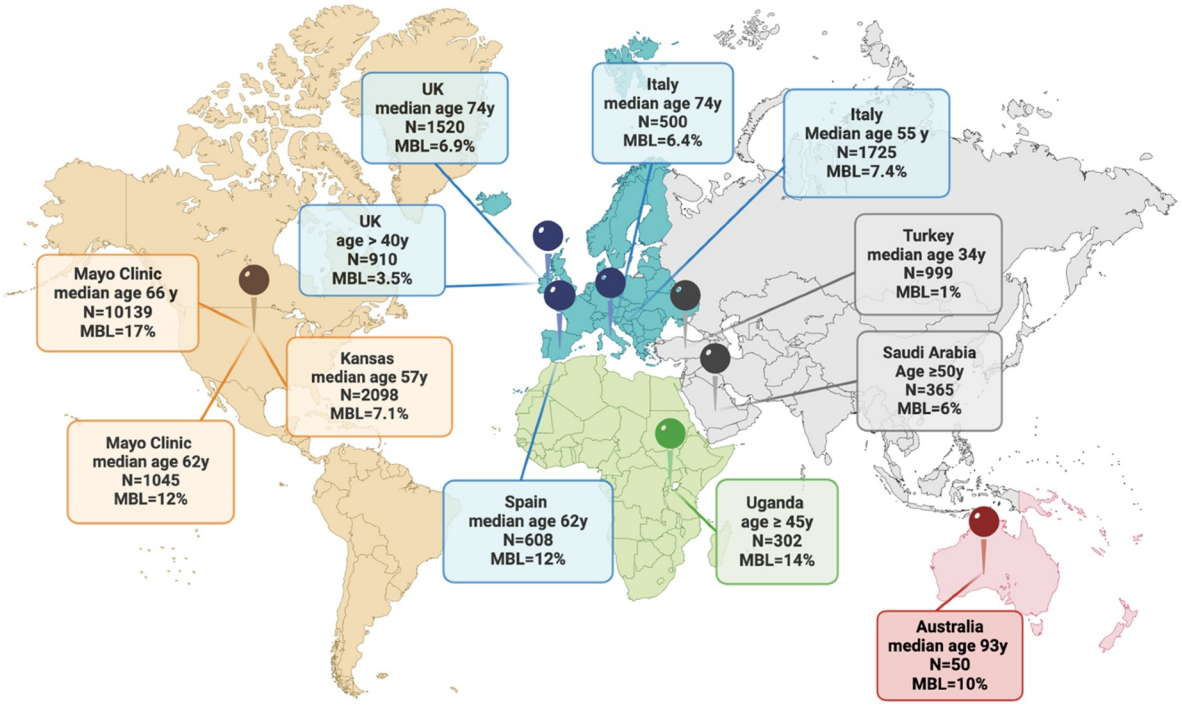

FIGURE 1 | Key studies assessing the incidence of MBL among healthy volunteers across various countries.

median of 7 years, found a significant reduction in OS compared to both non-MBL controls and the general population, particularly in females [22]. Interestingly, this study reported that infections and cancer were the leading causes of death in LC-MBL individuals, suggesting that while progression to CLL is rare, LC-MBL may serve as a marker of immune dysfunction, predisposing individuals to other comorbidities. Similarly, Shanafelt et al. reported that most cases of MBL (in this case mostly HC-MBL) do not progress to leukemia, individuals with MBL exhibit immune alterations that may contribute to increased susceptibility to infections and other malignancies [21].

3 | Familial Aggregation of MBL and CLL

There is compelling evidence that MBL and CLL share a strong familial component, with first-degree relatives of patients with CLL exhibiting a significantly higher prevalence of MBL than the general population [23–25]. One of the earliest studies to explore the familial basis of MBL and its relation to CLL was conducted by Rawstron et al. in 2002. They demonstrated that cells with CLL-phenotype could be detected in 13.5% of healthy first-degree relatives from CLL families; such prevalence was significantly higher than the one observed in the general population (3.5%), suggesting a sevenfold increased risk and for the first time highlighting the existence of a subclinical clonal B-cell expansion as an early premalignant stage in individuals with inherited predisposition [25]. This was followed by a larger investigation by Goldin et al. who screened 505 first-degree relatives from 140 high-risk CLL families, defined by the presence of at least two confirmed CLL cases per family, founding an MBL prevalence of 17% [23]. More recently, Slager et al. screened for MBL 1045 relatives from 310 families with at least two CLL cases [26]. The prevalence of MBL in these relatives was 22%, 10% more than what was observed in the general population [6, 10–12, 27, 28]. In addition, among familial cases with LC-MBL, the 5-year cumulative incidence of progression to CLL was reported to be 5.7%, significantly higher than previous estimates in non-familial cohorts, though one has to consider that the number of individuals observed was limited. It is interesting to hypothesize that, in a familiar context, LC-MBL may have a different biological set-up, following a linear trajectory, toward HC-MBL, and ultimately overt CLL.

4 | Molecular Characterization of MBL and CLL

At immunogenetic level, the immunoglobulin heavy chain variable region (IGHV) gene repertoire of HC-MBL and CLL are very similar, whereas LC-CLL appears like a distinct entity, expressing distinct IGHV genes (such as IGHV4-59) that are rarely seen in CLL [17, 29, 30].

An Italian study showed that all the recurrent chromosomal aberrations typical of CLL can be observed also in LC-MBL, including the infamous del (17p) as detected by fluorescence in situ hybridization (FISH) but at a significantly lower frequency compared to HC-MBL and CLL as confirmed by a Spanish study in 2013 [16, 17]. Similarly, HC-MBL and early stage CLL, including ultra-stable CLL (patients who do not progress for at least 10 years after diagnosis) but also LC-MBL look similar in their genetic set-up when analyzed by whole genome sequencing, all showing mutations in CLL driver genes although the variant allele frequency differs in the different conditions, progressively increasing from LC-MBL to overt CLL [31–34]. Further studies at a more granular resolution, such as higher sequencing depth, RNAseq and perhaps single cell analyses will possibly help to better elucidate the molecular differences between CLL, HC-MBL, and—in particular—LC-MBL. An additional finding of the WGS study was that some somatic mutations were shared between clonal B cells and the corresponding polymorphonuclear (PMN) cells, suggesting that a fraction of the mutations occur (before the disease onset) at the level of the hematopoietic stem cell (HSC) or a multipotent progenitor upstream of myeloid and lymphoid differentiation as also suggested by Damm et al. analyzing purified subpopulations of immune cells [31, 35].

More recently Sekar and colleagues focused on the analyses of mosaic chromosomal alterations (mCAs). These are somatic events in HSC which lead to the formation of a clonal subpopulation of mutated cells. They involve gain, losses and copy-number neutral loss of heterozygosity of large segments of DNA [36]. It has been found that the typical CLL-associated mCAs (deletions of 6q, 11q, 13q, 17p, trisomy 12, and CNN-LOH of 13q) were common in HC-MBL but rare in LC-MBL and non MBL subjects (specificity 99.9%) [37]. Furthermore, all individuals with CLL-associated mCAs had a mCAs cell fraction higher than the B-cell fraction, suggesting—again—a cell of origin prior to the B-cell lineage.

Albeit CLL is by definition monoclonal, MBL has been shown to be also oligoclonal, especially LC-MBL [38], with a clone size higher in monoclonal cases compared to oligoclonal LC-MBL [32]. Interestingly, the frequency of cytogenetic alterations as well as genetic complexity in both MBL and CLL clones from multiclonal cases was significantly lower than that of monoclonal cases. Oligoclonality might indicate the existence of a chronic antigen-driven immune response that precedes or accompanies the acquisition of genetic alterations and, rarely, progression [30].

Although there are positive associations with prior exposures to infectious agents (e.g. history of pneumonia) or cancers with the risk of developing MBL, the role played by environmental factors seem difficult to grasp being potentially acting through decades of the natural history of these conditions [19]. On the contrary genetic factors have been confirmed to be involved in the pathogenesis of MBL, though it remains to be understood how and which gene polymorphisms may impact on the immune function and activation, typical of the disease. A polygenic risk score (PRS) based on 41 SNPs, associated to CLL-susceptibility in a first cohort of European Ancestry (EA) individuals with MBL, have proven to significantly associate with MBL risk in a second cohort of mixed ancestries, while little evidence of the association between environmental factors and MBL risk was found [39]. The PRS-CLL score had higher values when progressing from controls to LC-MBL, to HC-MBL, to CLL. The PRS-CLL score was more significantly associated to MBL risk in the EA cohort compared to the African American ancestry, supporting the idea that the genetic background of the population under consideration must be taken in consideration [39].

Together with the inherited genetic predisposition, somatic gene variants contribute to the progression of MBL to CLL. The tumor mutation load (TML), estimated as the number of mutated genes among a panel of 59 recurrently mutated genes in CLL, was able to stratify the patients with MBL or CLL according to their risk to undergo treatment within a longitudinal cohort followed for 10 years [33]. For example, people with MBL, TML > 0, and high IPI-index (International Prognostic Index for CLL, defined using clinical features) have similar probabilities to undergo treatment compared to patients with CLL, suggesting that a more relevant role of the mutational status in determining the predisposition to progression compared to the specific diagnosis and/or the clinical features as identified by IPI classification.

5 | Clinical Implications of MBL

5.1 | Risk of Second Neoplasia

Several studies have reported an elevated risk of secondary malignancies among individuals with MBL, particularly melanoma and other skin cancers other than hematological cancers. The pathophysiological mechanisms underlying this increased cancer susceptibility are not fully understood but may involve immune surveillance defects, genetic predispositions, and chronic inflammatory states that facilitate tumor development. Vallejo et al. recently reported a nearly two-fold increased risk of developing melanoma among individuals with LC-MBL compared to the general population (1.86-fold for MBL overall, 1.92-fold for LC-MBL, who comprised the majority of the cohort) [40]. Moreover, individuals with LC-MBL showed a 2.74-fold increased risk of developing melanoma in situ, highlighting the possibility of underlying immune dysregulation as a contributing factor. MBL has also been associated with an increased risk of solid tumors such as lung cancer beyond skin cancers, and hematologic malignancies [41]. Intriguingly, in a recent retrospective study conducted at the Mayo Clinic, individuals with MBL/CLL had a significantly higher risk of venous thromboembolism (VTE), approximately six times higher than that of the age- and sex-matched general population, with no meaningful differences between MBL and CLL. However, in this cohort, 40% of VTE events occurred in individuals with a concomitant second malignancy, as a possible provoking factor [42].

Given these findings, individuals with MBL, particularly those with a history of skin cancer or strong familial cancer predisposition, should undergo enhanced cancer screening and dermatologic evaluations as part of routine follow-up.

5.2 | Immune Impairment and Infection Risk

Although several immunological deficiencies in both the innate and adaptive immune systems have been described in CLL, including hypogammaglobulinemia and compromised T- and NK-cell activity, the mechanisms leading to immune dysfunctions, particularly in the pre-leukemic phase, remain largely unknown [43, 44]. It is known that the absolute number of regulatory T cells (Tregs) increases in patients with CLL, and it has been shown that this number is lower in MBL subjects, compared to patients with CLL, but higher than in controls [45]. Moreover, the absolute number of Tregs directly correlated with more advanced Rai/Binet clinical stages, providing potentially an easy tool to monitor the immunological status of this disease through its different stages that need further prospective validation [45].

In addition, HC-MBL (and Rai 0-CLL) show reduced normal B cell counts, of both immature and naïve mature B lymphocytes, suggesting an impaired production of newly generated B cells in the bone marrow, even prior to the development of overt disease [46]. In HC-MBL both $CD4^+$ and $CD8^+$ T-cell clones have been detected and in particular the expansion of $CD4^+$ clones in parallel with the B-cell clone size [47]. Additionally, a reduction of circulating CD4+CD8+ double positive T-cells has been reported, suggesting impaired immunosurveillance, which could potentially promote the emergence of MBL clones [48].

Also LC-MBL cases show differences in T-cell subpopulations compared with healthy controls: T cells are, indeed, significantly increased, and T-cell expansions have been identified; studies are concordant on the increase of total T cells, $CD4^+$, and $CD8^+$, while the behavior of other T-cell subpopulations is still under debate [49, 50].

Such immune dysfunction may explain the higher rate of infections and autoimmune complications shared by patients with CLL and MBL [20].

Infections or infectious complications are, indeed, responsible for 30%–50% of all deaths in patients with CLL, and up to 50% of patients with CLL will develop infectious complications during the course of their disease [51]. Conversely, MBL, traditionally considered a benign precursor condition to CLL, is now more widely acknowledged for its own more hidden, but noteworthy, immune alterations.

The Mayo Clinic group demonstrated in their MBL population that the rate of hospitalization for infection in HC-MBL patients (around 16%) was approximately four times higher than the risk of progression to CLL requiring treatment after a median of 4 years from diagnosis [52]. This suggests that patients with MBL are at a higher risk of infectious complications than they are of progression.

More recently, in a study with 984 individuals screened for MBL, 106 (11%) were found to have LC-MBL CLL-like. The unadjusted estimated 8-year cumulative incidence of any infection, pneumonia, and bloodstream/sepsis were more prevalent among LC-MBL individuals. Additionally, the comprehensive co-morbidity assessment did not reveal any evidence of confounding caused by underlying health conditions that could account for this elevated risk [53].

A retrospective analysis of the Danish registry showed that the use of antimicrobials among patients with CLL increased gradually from 6 years before diagnosis. More importantly, they observed that patients had been using macrolides, antivirals,

and antimycotics more frequently than the population controls for 22 years before CLL diagnosis [54].

Recent evidence indicates that individuals with HC-MBL and CLL are at a significantly increased risk of adverse outcomes during the COVID19 pandemic [55]. Notably, also LC-MBL has been identified as an independent risk factor for severe infections and hospitalization [56]. Moreover, recovery of B-cell counts postinfection and the humoral response following SARSCoV2 vaccination are both impaired in these patients; although total antibody levels may eventually reach protective thresholds, the kinetics and quality of the response are suboptimal. Similar deficits in vaccine responsiveness have been observed in patients with HC-MBL following high dose influenza vaccination, pneumococcal vaccination, and recombinant herpes zoster vaccination [57–59]. Unfortunately, Whitaker et al. investigated only HC-MBL, and not LC-MBL, revealing a superior response compared to CLL but inferior to healthy controls [57]. Criado et al. proposed that HC-MBL exhibits immune deficiencies similar to CLL, unlike LC-MBL [58]. Muchtar et al. did not distinguish between HC-MBL and LC-MBL and analyzed MBL together with untreated CLL, reporting a reduced humoral and T-cell mediated response to VZV vaccine [59]. These findings collectively suggest that tailored vaccination strategies may be necessary to enhance protection in this vulnerable population.

6 | Conclusions

MBL constitutes a biological and clinical continuum with early-stage CLL, particularly for the HC-MBL subtype, which shares key prognostic markers and risk factors with stage 0 CLL. Beyond traditional prognostic models, the CLL-IPI score has shown predictive value in MBL, correlating with time to first therapy, while tumor mutation burden is emerging as another significant marker of disease progression [60]. Consequently, individuals with HC-MBL are generally advised to undergo lifelong clinical monitoring, including regular blood counts, thorough physical examination of superficial lymph nodes, and periodic abdominal ultrasound (where available) to detect deep lymphadenopathy. While MBL was initially studied for its potential progression to CLL, recent evidence highlights that risk of infections and second cancers is another critical concern. Given the reported impaired vaccine response in full-blown CLL, it is reasonable to expect that immunization during the MBL stage could provide more effective protection, though potentially not at the extent of the general unaffected population. Though no specific cancer screening protocols are recommended for MBL patients beyond those advised for the general population, we strongly encourage adherence to standard preventive measures, including routine colon, breast, and cervical cancer screening, skin examinations, sunscreen use, and smoking cessation. Importantly, LC-MBL is biologically distinct from HC-MBL and CLL, with a negligible risk of progression, and does not require clinical follow-up outside of research settings. These insights underscore the evolving understanding of MBL, not merely as a precursor of CLL but as a distinct clinical entity requiring tailored management strategies.

Author Contributions

All authors contributed to the writing, design, and revision of the manuscript, provided critical intellectual input, and approved the final version.

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Conflicts of Interest

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Data Availability Statement

The authors has nothing to report.

Peer Review

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