

Association of oxidative stress biomarkers with gene aberrations in chronic lymphocytic leukaemia

Viktoriya Varbanova¹, Margarita Alexandrova¹ , Vanya Slavcheva¹, Svetla Blazheva¹

¹ Medical University of Pleven, Pleven, Bulgaria

Corresponding author: Viktoriya Varbanova (viktorii.a.varbanova@mu-pleven.bg)

Summary

Chronic lymphocytic leukaemia (CLL) is one of the most common leukaemias in adults. Although extensive data on its pathogenesis and progression have accumulated, the disease remains chronic and incurable. Marked heterogeneity at every stage of CLL development limits the usefulness of routinely applied risk-stratification criteria. Published research suggests that the course of the disease is associated with oxidative stress and an increased frequency of cytogenetic aberrations. However, current evidence is insufficient to establish a causal relationship between these two factors. CLL patients exhibit a distinct antioxidant profile and decreased intracellular reducing potential. Moreover, levels of both early and late oxidative damage products are higher than normal. Concentrations of malondialdehyde and 8-oxo-dG have been reported to correlate with specific FISH-detected chromosomal aberrations. Future studies are needed to determine the extent to which oxidative biomarkers can improve the diagnostic and prognostic performance of routinely used biochemical and cytogenetic indicators in patients with CLL.

Key words: Antioxidants, chromosomal aberrations, CLL, mutagenesis, oxidative damage



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Introduction

Chronic lymphocytic leukaemia (CLL) is characterised by the expansion of monoclonal mature but dysfunctional B-lymphocytes in the blood, bone marrow, and secondary lymphoid organs of CLL patients (Mukkamalla et al. 2023; Koehrer and Burger 2024). It is one of the most common forms of leukaemia worldwide among older individuals. According to data from the Global Burden of Disease Study, the number of patients with CLL increased approximately 2.5-fold, and mortality increased by 107% between 1990 and 2019 (Ou et al. 2022). Given the rising global average life expectancy, CLL is expected to become a significant public health concern (Ou et al. 2022).

Despite the data accumulated in recent years on the pathogenesis and progression of CLL, the disease remains chronic and incurable. Some patients live for decades without therapy, while others die due to disease progression within a few years of diagnosis, despite treatment (Shahjahani et al. 2015).

The variable individual risk profile of CLL patients poses a challenge in predicting the disease course (Mollstedt et al. 2023). Currently, two clinical staging systems (Binet and Rai) are routinely used to stratify patients into different prognostic groups (Musolino et al. 2011). Unfortunately, each stage of CLL is too heterogeneous, making these criteria, especially when used alone, unsatisfactory for prognostic purposes (Collado et al. 2014). For this reason, it is necessary to identify new prognostic factors which, in addition to the classic ones, ensure reliable risk stratification of CLL patients at the time of diagnosis.

There is evidence that CLL progression is associated with an increased frequency of cytogenetic aberrations (Zhevak et al. 2020). Clinical studies indicate that at least one chromosomal deletion is present in 80% of untreated patients, and a combination of two or more chromosomal abnormalities is observed in 23% of them (Montague and Pathak 2023). Therefore, in 2016, an international prognostic index (IPI-CLL) was proposed, which, in addition to routine laboratory parameters, also includes data on the mutation status of genes encoding the variable region of heavy immunoglobulin chains (IGHV) (Molica et al. 2016).

According to recent studies, the presence or absence of gene aberrations is not sufficient to predict the course of the disease, as a group of patients exists in whom the clinical course does not correspond to the determined mutation status. The search for additional reliable biomarkers to enhance the prognostic value of the routinely used panel of biochemical data and cytogenetic tests in CLL patients continues (Hallek 2019, 2025).

Some authors consider oxidative stress (OS) a key factor in the aetiology and progression of CLL (Jitschin et al. 2014; Tannoury et al. 2024). OS is defined as a state of imbalance between the processes involved in the formation of reactive oxygen species (ROS) in the body and those that lead to their elimination (Demirci-Çekiç et al. 2022). The overproduction of reactive oxygen metabolites, when exceeding the capacity of the antioxidant defence system, can lead to oxidative damage to macromolecules and impaired cell signalling, the latter being the basis of the pathogenesis of various disease states. Studies suggest that OS contributes to genetic instability in CLL, but its role in the acquisition of specific cytogenetic aberrations remains unknown (Puiggros et al. 2014). On the other hand, genetic changes are responsible for increased ROS production *in vivo*, poor clinical outcomes, and patient resistance to treatment (Rigoni et al. 2015).

This narrative review aimed to investigate the potential relationship between biomarkers of oxidative stress and gene aberrations in patients with chronic lymphocytic leukaemia.

Materials and methods

We conducted a review of English-language articles available in the Scopus, PubMed, and Google Scholar databases. The search was performed using the following keywords: “oxidative stress,” “chronic lymphocytic leukaemia,” “chromosomal aberrations,” “prognostic markers,” “oxidative damage,” “antioxidants,” and “deletion.”

The criteria for inclusion of publications in the study, formulated in accordance with its purpose, are as follows: (1) articles investigating the effects of gene mutations and/or chromosomal aberrations on the levels of oxidative stress markers in newly diagnosed adult CLL patients; (2) original studies, narrative

and systematic reviews, and meta-analyses; (3) materials published in English in peer-reviewed and indexed journals between 2009 and 2024 (15 years).

We followed the guidelines for writing narrative reviews to prepare this manuscript (Baethge et al. 2019).

Chronic lymphocytic leukaemia - aetiology and prevalence

The etiopathogenesis of CLL is not fully understood. However, the main etiological factors are considered to be genetic predisposition, environmental factors, genetic and/or chromosomal abnormalities, and viral infections (Hallek and Al-Sawaf 2021). Studies have shown that the prevalence of CLL varies by geographic location and race (Mukkamalla et al. 2023). According to the literature, the average age of newly diagnosed patients is around 70 years. In cases of familial predisposition, CLL is transmitted to first-degree relatives about 20 years earlier than the parent's onset (Hallek and Al-Sawaf 2021). It is well established that the incidence of CLL increases with age (Tian et al. 2022; Siegel et al. 2023). Men are more affected than women, with a male-to-female ratio ranging from 1.3:1 to 1.7:1 in different populations (Mukkamalla et al. 2023). There is also evidence that the disease may be more aggressive in women (Kipps et al. 2017).

Genetic mutations and chromosomal aberrations in chronic lymphocytic leukaemia

Over the last decade, a large number of genes have been identified whose mutation influences the course and progression of CLL (Gaidano and Rossi 2017). The frequency of single somatic gene mutations in CLL is 1% to 5%. The number of gene mutations observed with high frequency in newly diagnosed patients is limited (Amin and Malek 2016). Mutations in the IGHV and TP53 genes have prognostic value and are included in the IPI-CLL index (Braish et al. 2024). There is also evidence that a large proportion of recurrent and relapsed gene mutations during CLL progression depend on IGHV mutation status (Mansouri et al. 2023).

Another manifestation of genetic abnormalities in CLL is the presence of chromosomal aberrations (CA). Clinical studies have reported at least one chromosomal deletion in 80% of newly diagnosed patients (Montague and Pathak 2023), and two or more chromosomal abnormalities in 23% of untreated patients (Zhevak et al. 2020). The most common chromosomal deletions are del(17p13), del(11q22), trisomy 12, and del(13q14), which are typically detected by FISH. Deletions on the short arm of chromosome 17 (del(17p13)) are often associated with a mutated TP53 gene and are found in 5% to 8% of untreated patients (Seiffert et al. 2012). Deletions on the long arm of chromosome 11 (del(11q22)) often cover the 11q23 band, which contains the ATM gene that encodes the proximal ATM kinase in response to DNA damage. This anomaly is found in approximately 10% of newly diagnosed patients (Döhner et al. 2000; Kröber et al. 2006; Parikh et al. 2016). Additionally, evidence indicates that trisomy 12 is present in 10% to 20% of CLL patients (Autore et al. 2018). Deletion of the long arm of chromosome 13 (del(13q14)) occurs in approximately 55% of all cases, making it the most common FISH-detected abnormality (Döhner et al. 2000). Approximately 20% of CLL patients do not exhibit FISH-identified chromosomal abnormalities, which is considered a favourable prognosis; however, it cannot be ruled out that patients may

carry other chromosomal abnormalities, as treatment outcomes within this group of patients are heterogeneous (Siegel et al. 2020). There is also evidence of other aberrations in CLL, which occur less frequently, in up to 5% of patients. For example, patients without FISH chromosomal abnormalities (Normal FISH result) may carry del(12p12) and translocations (t) of t(2;7)(p21; q32) (Rigolin et al. 2012).

It has also been found that the progression of CLL is characterised by a gradual increase in the frequency of chromosomal aberrations (from 64% in stage 0–1 to 75% in stage 4) (Zhevak et al. 2020). The presence of del(17p) is associated with a poor clinical outcome, whereas patients with del(13q14) are considered to have a more favourable prognosis (Puiggros et al. 2014). Furthermore, CLL patients with a mutated TP53 gene show resistance to chemoimmunotherapy. In contrast, those with only a non-mutated IGHV gene exhibit a delayed response to this type of treatment (Jondreville et al. 2020).

The different responses to treatment and varying disease courses, depending on the presence of gene mutations and/or CA, suggest their potential role in disease progression and clinical outcome.

Antioxidant status of patients with chronic lymphocytic leukaemia

Redox homeostasis is a prerequisite for normal cell function. The antioxidant defence system, which includes an arsenal of enzymatic and non-enzymatic antioxidants, plays a key role in maintaining it (Schieber and Chandel 2014; Rodríguez-García et al. 2020; Demirci-Çekiç et al. 2022). Published data indicate that reduced levels of some enzymatic antioxidants increase the risk of developing malignant diseases, while overexpression of others may be a consequence of tumour cell adaptation to oxidative stress (Sánchez-Martínez et al. 2016). Table 1 compares the levels of key enzymatic and non-enzymatic antioxidants in patients with CLL versus controls.

Table 1. Comparison of key antioxidants in CLL patients versus healthy controls.

Source	Patients/controls	Sample	SOD	GSH-Px	CAT	GSH	GSSG	GSSG/GSH	TAC
Carbonell et al. 2008	86/39	LYM	↓↓	↑↑	↓↓	↑↑	↑↑	↑↑↑	
Collado et al. 2012	55/31	LYM			↓↓↓	↑↑↑	↑↑↑	↑↑↑	
D'Arena et al. 2017	165/44	serum							↓↓↓
Jevtovic-Stoimenov et al. 2017	49/44	LYM		↑	↓				
Jitschin et al. 2014	25/16	mt	↓		↑↑↑				
Ortin et al. 2012	37/37	plasma				NS	↑	NS	
		Er	↑	↓	↑↑↑	↑	↑↑↑	↑	
Sabry et al. 2020	70/15	serum	↓↓		↓↓				
Saleem et al. 2022	60/30	serum							↓
Zelen et al. 2010	21/30	plasma	NS	NS	↑↑				
Zhevak et al. 2020	64/30	serum		↓					

Upward arrows (↑) indicate increased levels, downward arrows (↓) denote decreased levels. Single arrows (↑ or ↓) – $p < 0.05$, double arrows (↑↑ or ↓↓) – $p < 0.01$, triple arrows (↑↑↑ or ↓↓↓) – $p < 0.005$, and quadruple arrows (↑↑↑↑ or ↓↓↓↓) – $p < 0.001$.

CAT – catalase; Er – erythrocytes; GSH – reduced glutathione; GSH-Px – glutathione peroxidase; GSSG – oxidised glutathione; LYM – lymphocytes; mt- mitochondria; NS – not significant; SOD – superoxide dismutase; TAC – total antioxidant capacity.

Enzymatic antioxidants, which form the first line of defence against oxidative stress in the body, include superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px).

SOD is an enzyme antioxidant that catalyses the dismutation of the superoxide anion radical to hydrogen peroxide and harmless molecular oxygen. The role of SOD is crucial, as superoxide is constantly generated under physiological conditions in the body, including during mitochondrial ATP production. Published data on SOD levels in CLL patients are inconsistent (Table 1). Cu-Zn SOD activity was reduced in serum (Sabry et al. 2020) and lymphocytes (Carbonell et al. 2008), or remained unchanged in plasma (Zelen et al. 2010), compared to healthy individuals. On the other hand, reduced mitochondrial Mn SOD activity (Jitschin et al. 2014) and increased Cu-Zn SOD activity in erythrocytes (Ortin et al. 2012) were reported in patients compared to control groups. Some authors consider the reduction in SOD activity in the context of increased superoxide production in CLL (Cavallini et al. 2018), particularly increased mitochondrial oxidative phosphorylation in CLL cells (Jitschin et al. 2014; Dong et al. 2021). Other authors attribute the observed changes to an adaptive mechanism, resulting from the increased expression of the stress-sensitive enzyme heme oxygenase-1 (Jitschin et al. 2014). There is evidence that the expression levels of this enzyme influence mitochondrial biogenesis and hematopoiesis (Szade et al. 2021). Furthermore, a vicious cycle of increased ROS formation in mitochondria, mediated by increased mitochondrial biogenesis in CLL cells, has been hypothesised (Jitschin et al. 2014).

CAT is an antioxidant enzyme that decomposes H_2O_2 into water and triplet oxygen, preventing the formation of hydroxyl radicals ($\cdot OH$). Another enzyme that decomposes peroxides is GSH-Px. Unlike CAT, GSH-Px converts both inorganic and organic peroxides into harmless molecules using reduced glutathione (GSH) as a co-substrate. During the reaction, the latter is oxidised to glutathione disulfide (GSSG). The published data on CAT and GSH-Px activity in patients with CLL are inconsistent. Reduced CAT activity in the lymphocytes of patients with CLL compared to healthy individuals has been reported (Carbonell et al. 2008; Collado et al. 2012; Jevtovic-Stoimenov et al. 2017), but results for increased CAT activity in plasma (Zelen et al. 2010), mitochondria (Jitschn et al. 2014), and erythrocytes have also been published (Ortin et al. 2012). Regarding GSH-Px, increased enzyme activity has been found in lymphocytes (Jevtovic-Stoimenov et al. 2017), decreased activity in serum (Zhevak et al. 2020) and erythrocytes (Ortin et al. 2012), as well as no significant changes in plasma compared to healthy individuals (Zelen et al. 2010) (Table 1).

In the scientific literature, an increased GSSG/GSH ratio is often used as a biomarker of oxidative stress. In patients with CLL, significantly higher levels of both reduced and oxidised glutathione have been found in circulating lymphocytes (Carbonell et al. 2008; Collado et al. 2014) and erythrocytes (Ortin et al. 2012) compared to healthy subjects. Interestingly, the GSSG/GSH ratio is also elevated (Carbonell et al. 2008; Ortin et al. 2012; Collado et al. 2014), a marker of decreased intracellular reducing potential (Collado et al. 2014).

Only a limited number of studies have assessed serum total antioxidant capacity (TAC) in CLL. Two independent studies (D'Arena et al. 2017; Saleem et al. 2022) reported lower serum TAC levels in patients than in controls (Table 1).

Thus, CLL patients exhibit a distinct antioxidant profile, which is likely due to a combination of genetic, metabolic, and environmental factors (Ortin et al. 2012).

Potential relationship between antioxidant status and chromosome aberrations in chronic lymphocytic leukaemia

In recent years, indicators of mutations/aberrations/overexpression of specific genes and genetic variants, and overexpression of specific genes and glycoproteins have been used as biomarkers for CLL progression in clinical practice. However, published data on the association between these indicators and changes in the levels of key antioxidants are limited.

Zhevak et al. (2020) reported that serum GSH-Px activity correlated with disease stage. Nevertheless, no association has been found between this activity and IGHV mutation status. Another study found an association between GSH-Px activity in the lymphocytes of CLL patients and the presence of del(13q14) (Carbonell et al. 2008). There is also evidence that serum TAC cannot be used as a marker to distinguish patients with chromosomal deletions from those with Normal FISH results (D'Arena et al. 2017, 2019).

Regarding the overexpression of glycoproteins, it is worth noting that a negative correlation exists between TAC and the expression of the transmembrane protein CD200, which has been shown to have prognostic value in CLL (D'Arena et al. 2020). CD200 plays a role as an immunosuppressor of the body's T-cell response (Staub et al. 2021), which is thought to contribute to a faster progression and unfavourable disease outcome (Saleem et al. 2022).

Regarding genetic variants, it has been found that CAT activity in the lymphocytes of CLL patients is associated with the TNF genotype. In particular, patients with the TNF A (GA or AA) genotype show lower CAT activity than those with the TNF G (GG) genotype (Jevtovic-Stoimenov et al. 2017). Some authors suggest that the TNF-308A allele is a more potent activator of transcription in B cells than the more common TNF-308G allele; however, its involvement in CLL progression remains unclear (Zhou et al. 2017).

Currently, published data on the potential link between the levels of key antioxidants in CLL patients and gene mutations/aberrations, as well as the overexpression of specific genes/proteins, are too limited to allow drawing definitive conclusions.

Products of oxidative damage in patients with chronic lymphocytic leukaemia

A key feature of OS is the accumulation of oxidatively damaged biomolecules in the body. Lipid peroxidation (LP) is the predominant molecular mechanism through which ROS toxicity occurs. Conjugated dienes (CD) and malondialdehyde (MDA) levels are used as indicators of lipid peroxidation. CDs are formed as a result of the rearrangement of double bonds in polyunsaturated fatty acids during the early stages of lipid peroxidation. Published data indicate higher levels of CD in the serum of CLL patients compared to healthy individuals (Zhevak et al. 2020) (Table 2).

On the other hand, one of the end products of LP, MDA, is an important biomarker of oxidative stress. MDA is formed as a result of enzymatic and non-enzymatic peroxidation of polyunsaturated fatty acids containing at least three double bonds (Demirci-Çekiç et al. 2022). Higher MDA levels have been reported in the plasma (Zelen et al. 2010) and serum (Sabry et al. 2020; Zhevak et al. 2020) compared to healthy controls; however, there is also evidence of insignificant

Table 2. Comparison of oxidative damage marker levels in CLL patients versus healthy.

Source	Patients/controls	Sample	MDA	CD	PC	AOPPs	AGEs	8-oxo-DG
Carbonell et al. 2008	86/39	LYM	↑↑↑					↑↑↑
Collado et al. 2012	55/31	LYM	↑↑↑↑					↑↑↑↑
		urine						↑↑↑↑
Gangemi et al. 2012	60/23	serum				↑↑↑	↑↑↑	
Jevtovic-Stoimenov et al. 2017	49/44	LYM	↑↑↑↑					
Jitschin et al. 2014	25/16	mt	↑					↑
Musolino et al. 2011	48/30	serum			↑↑↑↑			
Ortin et al. 2012	37/37	plasma	NS					
		Er	↑↑↑↑					
Sabry et al. 2020	70/15	serum	↑↑↑↑		↑↑↑↑			
Saleem et al. 2022	60/30	serum	↑					
Zelen et al. 2010	21/30	plasma	↑↑↑↑					
Zhevak et al. 2020	64/30	serum	↑↑↑↑	↑↑↑↑				

Upward arrows (↑) indicate increased levels, downward arrows (↓) denote decreased levels. Single arrows (↑ or ↓) – $p < 0.05$, double arrows (↑↑ or ↓↓) – $p < 0.01$, triple arrows (↑↑↑ or ↓↓↓) – $p < 0.005$, and quadruple arrows (↑↑↑↑ or ↓↓↓↓) – $p < 0.001$.

AGEs – advanced glycation end products; AOPPs – advanced oxidation products of proteins; CD – conjugated dienes; Er – erythrocytes; 8-oxo-DG – eight-oxo-2'-deoxyguanosine; LYM – lymphocytes; MDA – malondialdehyde; mt – mitochondria; NS – not significant; PC – protein carbonyls.

changes in plasma MDA levels (Ortin et al. 2012). Higher MDA levels have also been reported in lymphocytes (Collado et al. 2014) and erythrocytes (Ortin et al. 2012) of CLL patients (Table 2). Furthermore, higher MDA levels have been found to correlate with higher serum CD levels (Zhevak et al. 2020).

It is essential to acknowledge that MDA may play a potential role in the pathogenesis of various diseases due to its ability to interact with oxidised proteins, forming advanced glycation end products (AGEs) and advanced oxidation of protein products (AOPPs) (Jové et al. 2020; Chaudhary et al. 2023). Over the past decade, special attention has been paid to these newer markers of oxidative stress (AGEs and AOPPs), as well as to the levels of carbonylated proteins (PC) and S-nitrosylated proteins (Rodríguez-García et al. 2020).

AGEs and AOPPs are products of the interaction between MDA and oxidised carbohydrates and proteins, respectively, which makes them stable and preferred oxidative biomarkers (Oltra et al. 2001; Imbesi et al. 2013). In CLL patients, elevated serum levels of AOPPs and AGEs have been found compared to the control group (Gangemi et al. 2012) (Table 2).

On the other hand, the presence of carbonylated proteins is associated with a possible loss of important protein functions due to their oxidative modification (Dong et al. 2021). Higher serum PC levels have been reported in CLL patients compared to healthy individuals (Musolino et al. 2011; Sabry et al. 2020) (Table 2). A positive association has been found between serum PC levels in CLL patients and the expression of the transmembrane glycoprotein CD38, as well as a negative association with the expression of the protein kinase ZAP70, which is involved in T-cell signalling.

Regarding DNA, 8-oxo-2'-deoxyguanosine (8-oxo-dG) is a widely used marker for oxidative damage. In patients with CLL, significantly higher levels of 8-oxo-dG have been reported in lymphocytes (Collado et al. 2014) and urine (Collado et al. 2014) compared with controls (Table 2).

Based on the published data on the presence of elevated levels of oxidative damage products in CLL patients, it can be concluded that these patients suffer from oxidative stress. It is assumed that this condition results from increased production of oxidants, reduced effectiveness of the antioxidant defence system and/or decreased effectiveness of the repair systems of oxidatively damaged biomolecules.

In summary, CLL patients have elevated levels of oxidative damage products compared to control groups, respectively, higher levels of OS. In particular, oxidative DNA damage in CLL patients is a prerequisite for genetic instability and the occurrence of chromosomal aberrations.

Potential relationship between oxidative damage products, gene mutations and chromosomal abnormalities in chronic lymphocytic leukaemia

As noted above, CLL patients show increased levels of oxidative stress products compared to healthy individuals. Limited data have been published on these levels in patients with chromosomal aberrations (Siegel et al. 2020). Fig. 1 presents a schematic comparison of MDA and 8-oxo-dG levels in patients with single deletions from the FISH panel versus those with a Normal FISH result. The data show that serum and plasma MDA levels in CLL patients with del(17p13) are higher compared to patients without FISH aberrations, but patients with del(11q22), trisomy 12, and del(13q14) show comparable levels to patients without deletions (Carbonell et al. 2008; Collado et al. 2012; Zhevak et al. 2020). However, changes in MDA levels in lymphocytes between patients with chromosomal aberrations are ambiguous. In particular, in patients with del(17p13), MDA levels are comparable to those in patients with negative FISH results, whereas in the other groups, MDA levels are reduced (Collado et al. 2014). It is noteworthy that lymphocyte MDA levels are higher in patients with a normal FISH result compared with those carrying the del(13q14) aberration, which is generally associated with a favourable prognosis. A possible explanation is that patients with normal FISH result may actually harbour additional, undetected chromosomal abnormalities (Collado et al. 2014). This interpretation is further supported by the elevated CD levels observed in patients with isolated del(17p13) as well as in those with multiple chromosomal aberrations (Collado et al. 2014).

Regarding 8-oxo-dG levels in lymphocytes of patients with chromosomal deletions, insignificant differences have been reported between patients with del(17p13) or del(11q22) and those without FISH-detected aberrations. In contrast, patients with del(13q14) or trisomy 12 exhibit reduced levels. No significant differences were found in 8-oxo-dG levels in the urine of patients with deletions and those without deletions from the FISH panel (Collado et al. 2014).

It is noteworthy that the number of published studies on the relationship between OS levels and chromosomal aberrations in patients with CLL is limited, making comparative analysis across groups difficult. At this stage, it can be assumed that OS levels are elevated in patients with del(17p13) or del(11q22) compared with those with del(13q14) and a normal FISH result. Additionally, given that del(17p13) is considered a marker of poor clinical outcome in CLL patients (Delgado et al. 2012), a potential role of OS in CLL progression can be inferred (D'Arena et al. 2017).

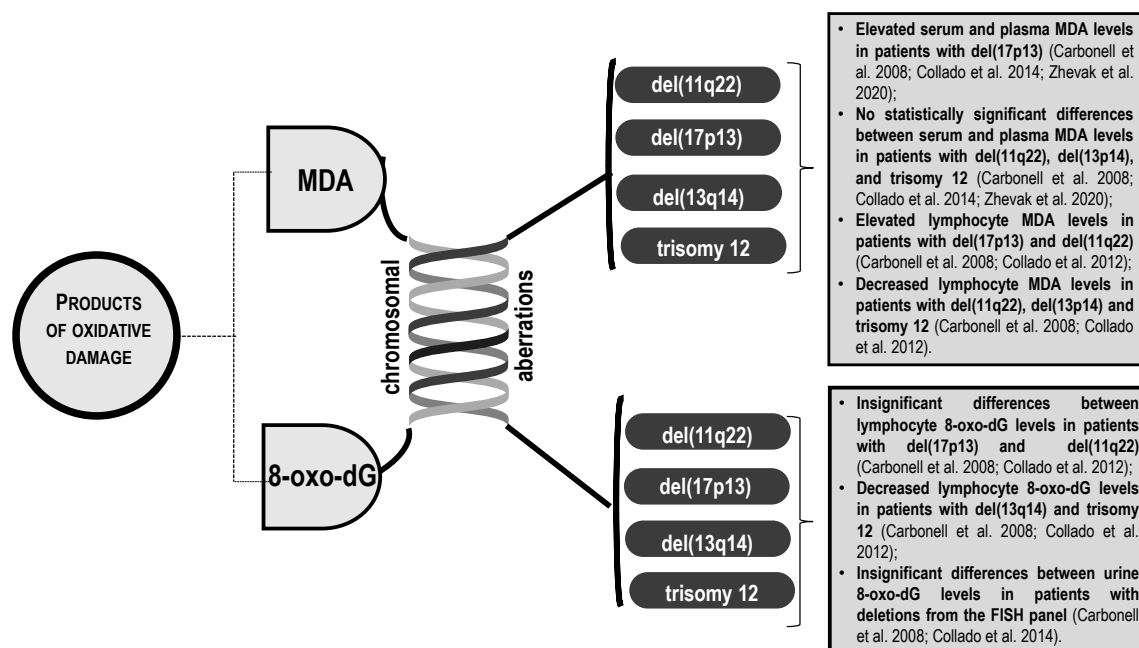


Figure 1. Markers of oxidative damage in patients with chromosomal aberrations compared to patients with normal FISH result. 8-oxo-DG – eight-oxo-2'-deoxyguanosine; MDA – malondialdehyde.

Conclusion

Many studies have examined the contribution of oxidative stress to the pathogenesis and progression of chronic lymphocytic leukaemia. The available data clearly indicate that CLL patients experience increased oxidative stress. Elevated levels of oxidative damage products in these patients may result from reduced effectiveness of the antioxidant defence system, increased ROS production, and/or adaptive mechanisms that allow CLL cells to survive under conditions of chronic oxidative stress, thereby promoting resistance to apoptosis.

Despite extensive research, the causal role of OS in CLL and the therapeutic potential of modulating oxidative pathways remain unresolved. The involvement of multiple mechanisms in ROS generation, along with the body's capacity to counteract or even adapt to oxidative stress, makes interpreting findings complex and sometimes contradictory. Evidence regarding the relationship between a patient's cytogenetic profile, OS levels, and CLL progression is similarly limited and inconsistent.

Further studies are required to determine the extent to which oxidative biomarkers could enhance the diagnostic and prognostic value of routinely used laboratory and cytogenetic tests in CLL. From a clinical perspective, integrating detailed cytogenetic profiling with a better understanding of OS-related mechanisms during targeted therapy could help identify whether oxidative damage products may serve as valuable biomarkers for personalised treatment strategies.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

No use of AI was reported.

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Author contributions

Conceptualization: SB, MA, VS. Writing - original draft: VRV. Writing - review and editing: MA, VRV, VS, SB.

Author ORCIDs

Margarita Alexandrova  <https://orcid.org/0000-0003-1180-9414>

Data availability

All of the data that support the findings of this study are available in the main text.

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