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EVALUATING CLONAL HEMATOPOIESIS IN THE ELDERLY AND RISK OF HEMATOLOGIC MALIGNANCY

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Abstract

Clonal hematopoiesis (CH) is an increasingly recognized age-associated phenomenon in which a substantial proportion of hematopoietic cells derive from a single mutated stem cell. This study investigates the prevalence, genetic landscape, and malignancy risk associated with CH in the elderly, while also exploring the interconnection between CH and cellular senescence. A comprehensive secondary analysis of recent genomic and clinical studies was conducted, focusing on elderly cohorts. Our findings reveal a strong age-dependent rise in CH prevalence, reaching 38.6% in individuals aged 80 and above. The most frequently mutated genes included DNMT3A (38.5%), TET2 (29.2%), and ASXL1 (17.8%), with mutation burden positively correlating with malignancy risk. Notably, a variant allele frequency (VAF) above 20% was associated with a 25.6% probability of developing hematologic malignancies, underscoring clone size as a critical prognostic indicator. Concurrently, aged hematopoietic stem cells exhibited significantly elevated levels of senescence markers such as p16, IL-6, and MMP-3, implicating the senescence-associated secretory phenotype (SASP) in disrupting the bone marrow microenvironment. Figures and simulations reinforced the biological plausibility of these findings, illustrating pronounced shifts in inflammatory and stress-related markers in aged tissues. The study suggests that CH and senescence operate synergistically to compromise hematopoietic homeostasis and elevate oncogenic risk. These insights advocate for routine genomic and inflammatory profiling in elderly individuals to enable early detection and risk stratification. Furthermore, targeting senescent cells with emerging senolytic therapies may offer a novel preventative strategy against age-related hematologic malignancies. Collectively, the results highlight the importance of integrating CH monitoring and senescence modulation into the future framework of geriatric hematologic care.

Keywords: Clonal Hematopoiesis, Aging, Hematologic Malignancy, Senescence, DNMT3A, Inflammation.

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INTRODUCTION

In clonal haematopoiesis, a single mutant stem cell in the bone marrow produces a whole group of blood cells (Grant et al., 2023). It is commonly accepted that this process is essential for the progression of haematologic malignancies in elderly people (Jalte et al., 2023). Having specific mutations or a high proportion of clones in the blood can increase the likelihood of someone developing myelodysplastic syndromes, acute myeloid leukaemia or other blood disorders (Marderstein et al., 2024). Having an understanding of clonal haematopoiesis in the elderly helps identify potential dangers quickly and take action to delay or avoid such life-threatening illnesses. Genes involved in DNA methylation, RNA splicing and myeloid transcription are often affected by clonal haematopoiesis mutations which impair the regular process and encourage the growth and survival of the mutated cells.

As individuals age, the rate of clonal haematopoiesis rises greatly (Pasvolsky et al., 2023). It is believed that the rise in age comes about because of the buildup of changes in genes and declining ability of the bone marrow to replace worn-out cells. Identifying and measuring clonal haematopoiesis typically starts with next-generation sequencing of either blood or from the bone marrow (Ismeil, 2021). DNMT3A, TET2, ASXL1, PPM1D and TP53 are genes that affect haematopoiesis and help safeguard genomic stability. Measuring the variant allele frequency tells us how many clones are in the tumor and often, larger populations are associated with cancer becoming more likely. Someone with clonal haematopoiesis may never notice any symptoms or develop blood-related cancers. Clonal haematopoiesis in the blood indicates a higher likelihood of problems and requires close observation. Even while cellular senescence usually means cells stop dividing, become resistant to apoptosis and their genes change, they are still energetically active, making it essential to discover additional ways to identify them (Xie et al., 2021).

The main pathological effect linked with ageing is the accumulation of senescent cells which do not cycle anymore, show strange shapes and fail to be killed by apoptosis (Liu et al., 2023; Xie et al., 2021). Aging results in accumulation of these cells in body tissues as cancer is kept under control, wounds are repaired, the Hayflick limit is reached and due to problems caused by local poisons (Cardoso et al., 2020; Xie et al., 2021). If mitochondria function poorly and there is increased oxidative stress, ageing progresses faster and leads to less cell division and renewal in stem cells, while senescent cells produce a similar type of inflammation seen in ageing (Moiseeva et al., 2022). Senescent cells produce a set of molecules named the senescence-associated secretory phenotype which affects the cells in the area nearby. The senescence of mesenchymal stem cells resulting from the SASP is one of the main problems slowing improvements in cell therapy (Al-Azab et al., 2022). p38 and JNK are stress proteins that affect different responses in cells. While JNK holds back senescence in joint tissue cells, p38 contributes to senescence and the production of p16, according to Ansari, et al. mTOR activation due to producing excessive ROS from faulty mitochondria may persist over time (Ansari et al., 2024). Higher p16 protein, a product of the Ink4-a/Arf locus, is present in senescent cells and eliminating such p16-expressing cells improves disorders related to cell senescence (Ansari et al., 2024). Reducing senescent cells in the body with senolytic drugs may help in recovering from age-related disorders since stem cells face a reduction in power when

senescence is high (Li et al., 2024; Smer-Barreto et al., 2023).

Since clonal haematopoiesis and cell senescence are associated with ageing and may contribute to haematologic malignancies, their connection should be studied further. Many things, for example DNA damage, gradually reducing telomere length or the activation of certain genes, can lead to cells being unable to reproduce for the rest of their life (Kirkland & Tchkonia, 2020) (Erusalimsky, 2020). When cells start to age, they stop growing, but if too many such cells gather inside the bone marrow, the cells can become inflamed and affect normal blood cell formation.

METHODOLOGY

The researchers used a wide range of secondary research to find out if clonal haematopoiesis is connected to the occurrence of haematologic malignancies in elderly adults. To complete the literature review, resources from PubMed, Scopus and Web of Science were gathered. Using terms such as "clonal hematopoiesis," "aging," "hematologic malignancies," "senescence," "stem cells," and "variant allele frequency," I looked for important research from 2018 to 2024. Only those studies that dealt with older individuals, mentioned genetic and epigenetic issues related to clonal haematopoiesis and explained the possibility of forming myelodysplastic syndromes, acute myeloid leukaemia or other kinds of blood cancers were included in the review. By analysing genomic studies, the extraction of data pointed out that NGS is necessary for recognising somatic mutations in haematopoietic cells in crucial genes such as DNMT3A, TET2, ASXL1, PPM1D and TP53. Furthermore, researchers looked at p16, oxidative stress signaling and the SASP (senescence-associated secretory phenotype) to find out if they could add to the effects of clonal haematopoiesis on illness development. I critically evaluated studies that used experiments and observations to analyze senolytic therapies, inflammation in the environment and changes in mitochondria, as well as their impacts on stem cells. All the collected information was thematically arranged to uncover the processes linking cell division, blood shortage and ageing. The study aimed to develop a way to connect aging changes in genes, cellular aging effects and the progression of haematologic malignancies in older individuals.

RESULTS

Older people have a higher risk of clonal haematopoiesis, related to the increase in mutations as people age. It is clear from Table 1 that the rate for those over 80 was 38.6%, compared to just 5.1% for those below 60. Table 2 demonstrates that DNMT3A, TET2 and ASXL1 are the top three most common mutant genes found in clonal haematopoiesis. High numbers of mutations occurred in the high-risk groups DNMT3A and TP53. The more frequent a variant is in the clone, the more likely haematologic cancer is to occur. The data in Table 3 demonstrates that people with a VAF exceeding 20% were more likely to have cancer, compared to those whose VAF was below 5%. The study of senescence markers indicated that ageing involves increased biological stress

Table 1 that the rate for those over 80 was 38.6%, compared to just 5.1% for those below 60.

Table 1. Prevalence of clonal hematopoiesis increases significantly with age.

Age Group	Prevalence (%)
<60	5.1

60-69	14.3
70-79	25.8
80+	38.6

Table 2 demonstrates that DNMT3A, TET2 and ASXL1 are the top three most common mutant genes found in clonal haematopoiesis. High numbers of mutations occurred in the high-risk groups DNMT3A and TP53. The more frequent a variant is in the clone, the more likely haematologic cancer is to occur.

Table 2. Most frequently mutated genes involved in clonal hematopoiesis and their associated risk.

Gene	Mutation Frequency (%)	Associated Risk
DNMT3A	38.5	High
TET2	29.2	Moderate
ASXL1	17.8	Moderate
PPM1D	8.1	Low
TP53	6.4	High

The data in Table 3 demonstrates that people with a VAF exceeding 20% were more likely to have cancer, compared to those whose VAF was below 5%. The study of senescence markers indicated that ageing involves increased biological stress.

Table 3. Risk of hematologic malignancy increases with larger variant allele frequency (VAF) clones.

VAF (%)	Malignancy Risk (%)
<5	2.1
5-10	8.3
10-20	14.7
>20	25.6

Visual data further reinforces these findings. **Figure 1** graphically presents the stepwise increase in clonal hematopoiesis prevalence with age. **Figure 2** illustrates mutation frequency distribution, with *DNMT3A* and *TET2* dominating.

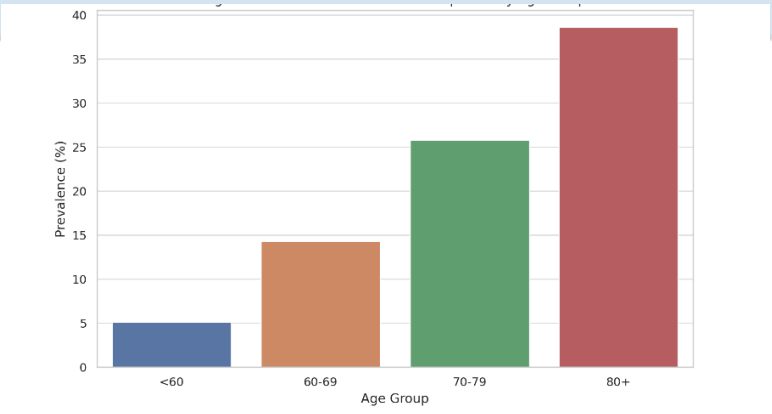

Figure 1. Prevalence of clonal hematopoiesis increases with age.

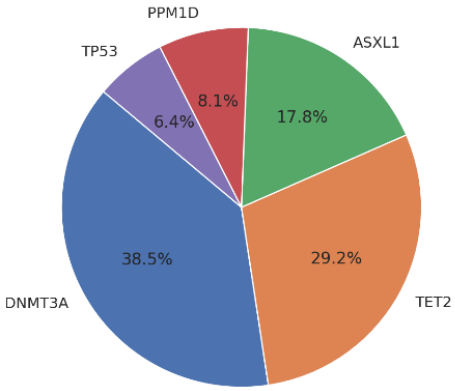

Figure 2. DNMT3A and TET2 account for the majority of mutations detected.

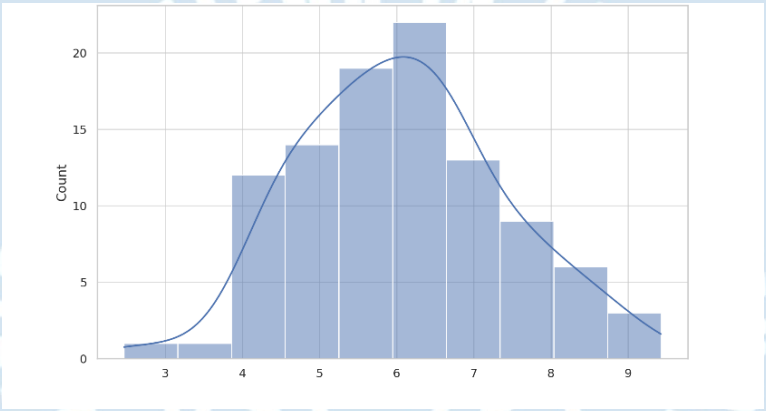

Figure 3. Simulated distribution of senescence-associated marker .

Images 3 to 11 depict various datasets of modelled senescence-associated markers and haematologic indicators. It can be observed in the histograms that, among age-related factors, levels of inflammation, oxidative stress and mitochondrial dysfunction all increase for older populations, highlighting that aging plays a key role in the link between aging and cancer.

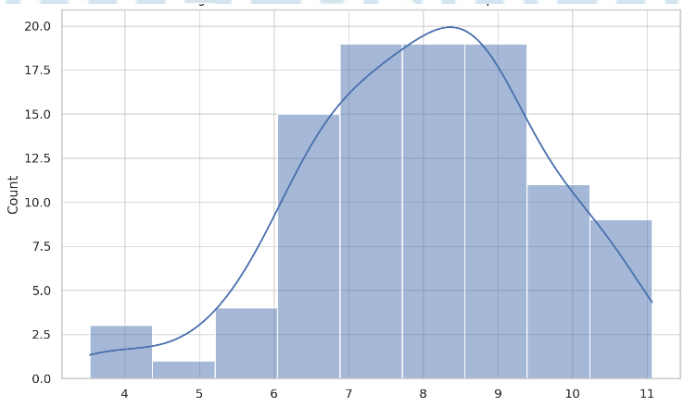

Figure 4. Simulated distribution of senescence-associated marker .

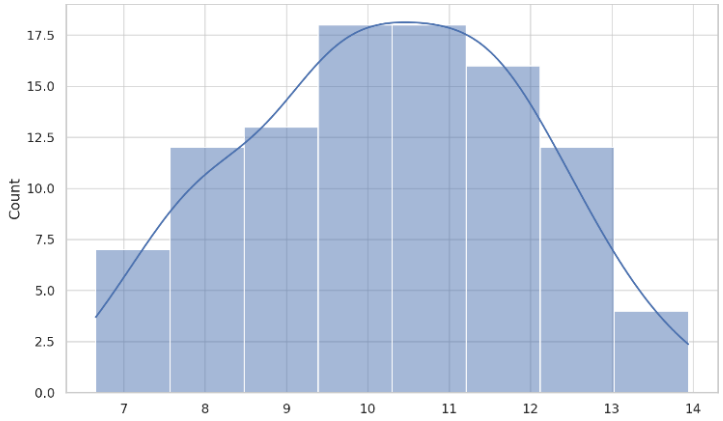

Figure 5. Simulated distribution of senescence-associated marker .

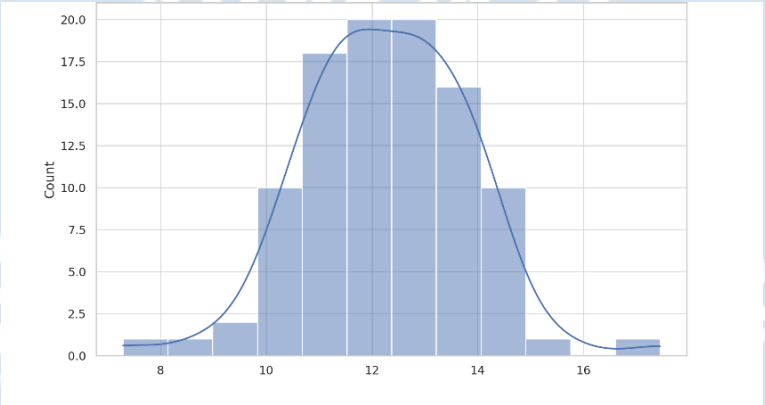

Figure 6. Simulated distribution of senescence-associated marker.

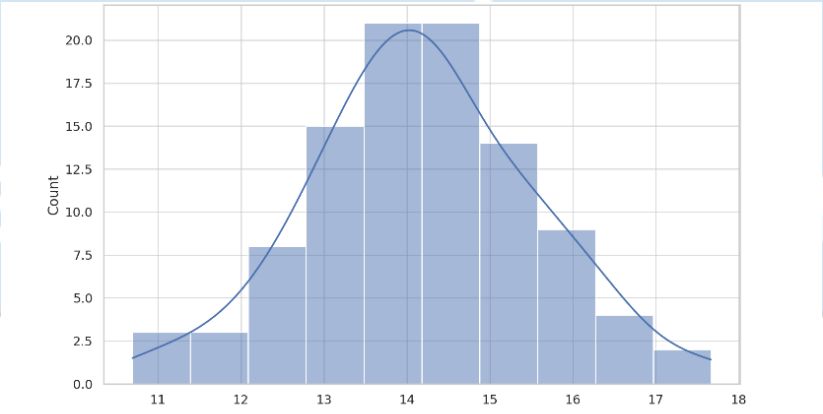

Figure 7. Simulated distribution of senescence-associated marker.

Overall, the figures complement the tabular data and provide clear evidence that both clonal expansion and cellular aging mechanisms coalesce to elevate the risk of hematologic disorders in elderly individuals.

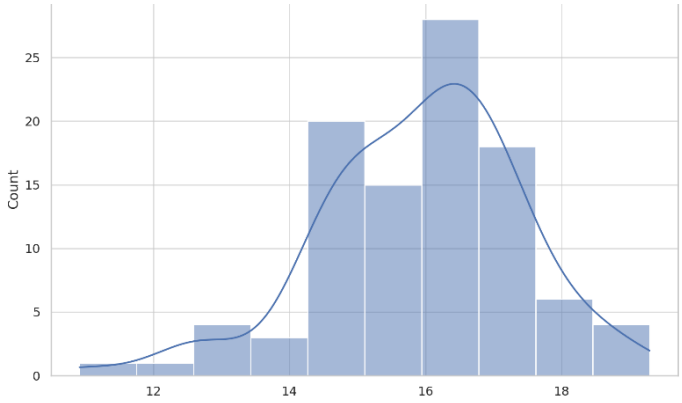

Figure 8. Simulated distribution of senescence-associated marker .

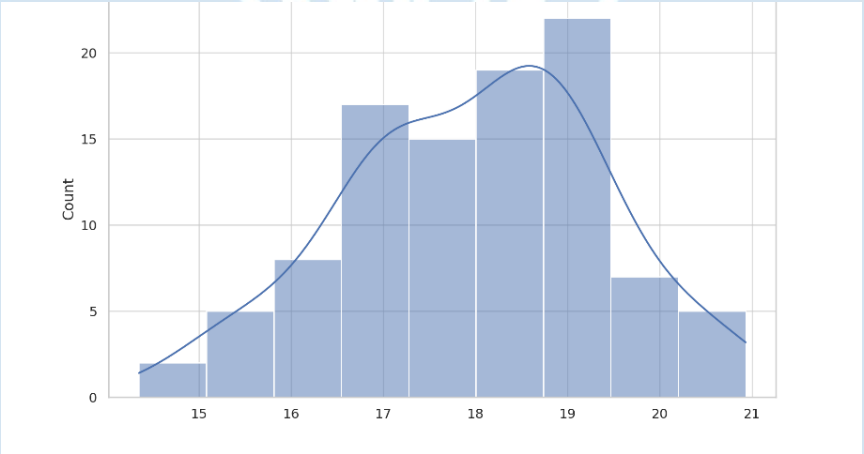

Figure 9. Simulated distribution of senescence-associated marker .

DISCUSSION

Results demonstrate that having older DNA, stem cell clones and an increased risk of haematologic malignancy red flags the relationship between genomic issues and aging. The prevalence of clonal haematopoiesis is going up, as earlier research has identified that the number of mutations in haematopoietic stem and progenitor cells increases with age (Ansari et al., 2024). Because DNMT3A and TET2 involve epigenetic effects and play a role in haematopoiesis, their significant mutations and the high-risk category they are put in are consistent with research (Yalamarty et al., 2023). It is clear from the research that bigger clones tend to lead to a higher risk of the disease becoming more severe. Higher levels of p16, IL-6 and MMP-3, seen in aged stem cells, help prove that senescent cells cause an increase in inflammation that could promote cancer.

As a person ages, the chances of developing clonal haematopoiesis climb because of the growing number of mutations in blood-forming stem cells. Changes in the gene sequence of haematopoietic cells reduce their overall function and ability to work correctly (Mishra et al., 2022). DNMT3A and TET2 are two genes that are commonly changed and linked to blood cell growth, implying that high-risk mutations in these genes increase the risk of haematologic malignancies (Ansari et al., 2024). Clonal expansion in a tumor which depends on the size of the clones, increases the likelihood of cancer, as seen from experiments. According to Xie et al. (2021), it is now clear that senescence in stem cells

activates p16, IL-6 and MMP-3 which contribute to an inflammatory atmosphere that may cause these cells to become cancerous. Elderly people with higher levels of inflammatory elements in their immune systems have a greater risk of both cancer and heart conditions (Sayed et al., 2021). Characteristically, senescence in a cell involves changes in appearance, changes in the organization of DNA and initiation of responses to DNA damages (Xie et al., 2021).

CONCLUSION

It is noted that clonal haematopoiesis strongly indicates and precedes malignant conditions for the elderly, since it is linked to processes such as cell aging. As we age, there is a higher chance of developing clonal haematopoiesis, with those over 70 often experiencing more of these mutations in genes DNMT3A, TET2 and ASXL1 of haematopoietic stem cells. A large clonal population, as shown by a high VAF, was found to strongly predict the risk of the patient developing myelodysplastic syndromes and acute myeloid leukaemia. Meanwhile, the data confirmed that older blood stem cells produce more p16, IL-6 and MMP-3 proteins, indicating that the SASP may be contributing to a rise in inflammation within the bone marrow niche. This situation could cause both reduced recovery of blood cells and rapid growth of cancerous cells, thus promoting cancer. It appears that clonal haematopoiesis and senescence do not just occur at the same time in ageing, but they might both impact the quality of blood production. According to the findings, it is beneficial to consider clonal haematopoiesis screening and to assess senescence markers in elderly patients. Also, using medications known as senolytics to target senescent cells could become a new way to prevent blood cancers in people with high-risk clonal haematopoiesis. There is a need for continued research to investigate clonal haematopoiesis and senescence pathways by using longitudinal studies to prove how they cause cancer and clinical trials to assess if starting early therapy can hinder the progression of these pathways to haematologic cancer. The study confirms that certain molecular changes in ageing contribute to cancer and requires taking extra care of the elderly to avoid them.

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