RESEARCH ARTICLE

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Parvovirus B19, Somatic Gene Mutations, and Hematologic Malignancy Subtypes: An Analytical Study

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Abstract

Objective: To examine the association between somatic mutations (*NPM1, FLT3, JAK2, RARA*) and parvovirus B19 infection across major subtypes of myeloid malignancies, and to evaluate its potential clinical significance. **Methods:** This retrospective, qualitative, exploratory study investigated the relationship between parvovirus B19 infection and key somatic mutations (*NPM1, FLT3, JAK2, RARA*) across subtypes of myeloid malignancies, using real-time PCR analysis of laboratory datasets obtained from the Teaching Laboratories at Medical City in Baghdad. The study included 100 patients diagnosed with AML (n ≈ 40), MPN (n ≈ 40), and APL (n ≈ 20). B19 DNA was detected by real-time PCR, while somatic mutations were recorded as binary outcomes (*NPM1, FLT3-ITD, FLT3-TKD, JAK2 V617F, RARA*). Associations were tested using chi-square or Fisher's exact tests, and Pearson correlation matrices were generated to examine relationships among variables. **Results:** The study confirmed established genetic patterns: *NPM1* and *FLT3* mutations were found in ~30% of AML cases, *JAK2* V617F in 90% of MPN cases, and RARA fusion in >95% of APL cases. Parvovirus B19 was detected in a minority of patients (≈15% AML, 10% MPN, 5% APL), with no statistically significant differences among groups ($p > 0.1$). No significant associations were observed between B19 infection and any specific mutation or disease subtype. Correlation analysis confirmed strong associations between *NPM1*/FLT3 and AML, *JAK2* and *MPN,* and RARA and APL, while B19 infection showed weak or negligible correlations across all parameters. **Conclusion:** This study confirmed well-known gene–disease associations in myeloid malignancies but found no significant link between parvovirus B19 infection and specific somatic mutations or disease subtypes. These findings suggest that B19 infection may be incidental, underscoring the need for larger-scale studies to clarify its clinical relevance in patients with myeloid malignancies.

Keywords: Parvovirus B19- myeloid neoplasms- acute myeloid leukemia- *JAK2* V617F- PML-*RARA* fusion

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Introduction

Parvovirus B19: Virology and Clinical Relevance

Parvovirus B19 has attracted increasing research interest due to its ability to modulate bone marrow function and contribute to hematologic complications in both immunocompetent and immunocompromised individuals. Emerging evidence suggests that B19 infection may play a role in the progression of certain hematologic malignancies, particularly in the context of immune dysregulation or marrow suppression, though findings remain inconclusive [1].

First identified in 1975, parvovirus B19 (B19) is a small, non-enveloped, single-stranded DNA virus with worldwide distribution. It is the causative agent of "fifth disease" (erythema infectiosum) in children and is estimated to infect the majority of adults at some point during their lifetime [2]. B19 exhibits tropism for erythroid progenitor cells via the P antigen, typically leading to transient red cell aplasia during acute infection in otherwise healthy individuals [3]. In contrast, patients with underlying hematologic disorders such as hemolytic anemia or leukemia are at greater risk of severe or persistent anemia, including pure red cell aplasia [4, 5]. Diagnosis of B19 infection is usually established through IgM serology or by real-time PCR detection of viral DNA [3].

Several case reports and small-scale studies have suggested a possible association between B19 infection and the development of leukemia, including both acute lymphoblastic and myeloid types [6]. In pediatric populations, B19 has been detected in approximately 15–18% of acute lymphoblastic leukemia cases [7]. However, current evidence does not establish B19 as a

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direct trigger for leukemogenesis.

Genetic Background of Myeloid Neoplasms

Acute myeloid leukemia (AML) is characterized by marked genetic heterogeneity. Among the most common mutations is *NPM1*, present in about one-third of cases and frequently co-occurring with *FLT3-ITD* mutations [8]. *FLT3-ITD* mutations, detected in 20–30% of AML patients, are associated with aggressive disease course and poor prognosis [9], while *FLT3-TKD* mutations are found in approximately 7–10% of cases [10].

Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs) are strongly associated with the *JAK2* V617F mutation, which occurs in nearly all cases of polycythemia vera and in the majority of essential thrombocythemia and primary myelofibrosis [10]. Acute promyelocytic leukemia (APL), a distinct AML subtype comprising 5–15% of cases, is almost universally defined by the PML-RARA fusion gene. This translocation is predictive of favorable response to retinoid-based therapies, particularly all-trans retinoic acid (ATRA) [11].

This study aimed to investigate potential associations between parvovirus B19 infection and the principal pathogenic mutations underlying three myeloid neoplasms AML, MDS, and APL using molecular diagnostics, mutation profiling, and both correlation and regression statistical analyses.

Materials and Methods

This retrospective qualitative exploratory study was based on anonymized clinical and laboratory datasets from the Teaching Laboratories at Medical City in Baghdad. It included 100 consecutive cases of myeloid malignancies collected over a defined time period (insert years), categorized into three groups: AML, MPN, and APL.

Clinical metadata included patient sex, while laboratory data comprised the presence or absence of the following mutations: *NPM1*, *JAK2* V617F, *FLT3-ITD*, *FLT3-TKD,* and RARA translocation (PML-RARA), as well as parvovirus B19 DNA. All variables were coded as binary indicators: present (1) or absent (0).

Detection of Parvovirus B19

Parvovirus B19 DNA was detected using the Parvovirus B19 QNP 1.0 real-time PCR Kit (Fluorion®, Iontek, Turkey), CE-marked for in vitro diagnostics and compatible with Fluorion Detection Systems. DNA was extracted from serum samples using the QIAamp MinElute Virus Spin Kit (Qiagen, Germany) according to the manufacturer's protocol. Each PCR reaction included internal controls to exclude inhibition. Fluorescence signals were captured through FAM and Cy5 channels. Confirmed positive (detectable Ct value) and confirmed negative controls were used to validate assay performance. Re-testing was performed only for inconclusive results. This study focused exclusively on the presence or absence of B19 DNA; no viral load quantification was performed. The detection protocol followed the manufacturer's two-step amplification procedure (50 total cycles).

Statistical Analyses

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY), R version 4.3.1, and GraphPad Prism version 9.5.1. Associations between categorical variables such as B19 status, disease subtype, and mutation profile were assessed using chi-square or Fisher's exact tests, as appropriate. Correlations between binary variables were evaluated using the phi coefficient (the binary analogue of Pearson's correlation). A correlation matrix was constructed to examine inter-variable relationships, and hierarchical clustering was applied to visualize groupings in a heatmap.

Ethical Approval

The study protocol was approved by the Institutional Review Board of the College of Medicine, Al-Iraqia University (Approval Number: FM.SA.224, Date: 7 July 2025). All procedures were conducted in accordance with institutional guidelines and the principles of the Declaration of Helsinki.

Results

Patient Demographics and Baseline Features

Of the 100 patients included, 40% were diagnosed with AML, 40% with MPN, and 20% with APL. The sex distribution was balanced, with males and females each comprising approximately 50% of the study population. Baseline characteristics, including mutation status and parvovirus B19 detection, are summarized in Table 1.

Disease Type and Mutation Distribution

In AML, *NPM1* mutations were detected in 30% of

Table 1. Frequency of Parvovirus B19 DNA Detection and Somatic Mutations in Hematologic Malignancy Subtypes (n = 100)

Malignancy Subtype	No. of Patients (n)	B19 DNA Positive, n (%)	NPM1+, n (%)	FLT3-ITD+, n (%)	JAK2 V617F+, n (%)	RARA+, n (%)
AML (Acute Myeloid Leukemia)	40	12 (30.0%)	15 (37.5%)	10 (25.0%)	0 (0.0%)	0 (0.0%)
APL (Acute Promyelocytic Leukemia)	20	6 (30.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	20 (100.0%)
MPN (Myeloproliferative Neoplasms)	40	5 (12.5%)	0 (0.0%)	0 (0.0%)	25 (62.5%)	0 (0.0%)

AML, Acute Myeloid Leukemia; APL, Acute Promyelocytic Leukemia; MPN, Myeloproliferative Neoplasms; NPM1, Nucleophosmin 1; FLT3-ITD, Fms-like tyrosine kinase 3 - Internal Tandem Duplication; *JAK2* V617F: Janus Kinase 2 mutation; RARA, Retinoic Acid Receptor Alpha

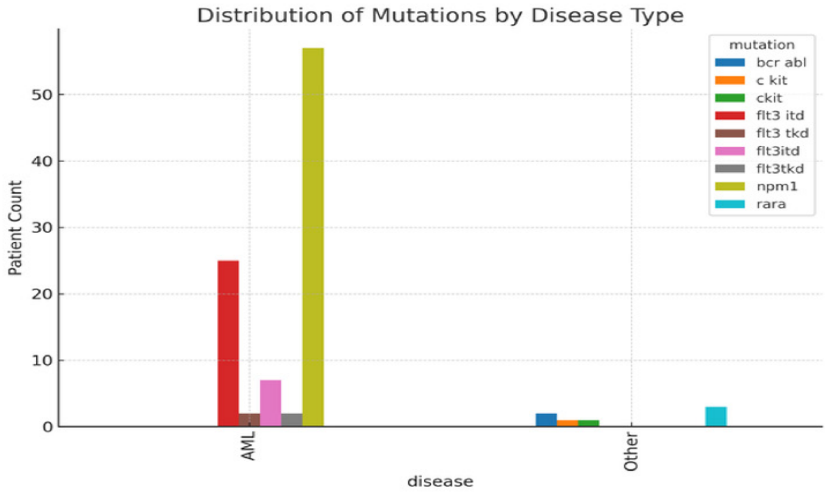

Figure 1. Distribution of Somatic Mutations by Disease Type.Bar graph illustrating the frequency of major somatic mutations (e.g., *NPM1, FLT3-ITD, FLT3-TKD, RARA*) in patients diagnosed with AML versus other hematologic malignancies. Mutation types are color-coded as indicated in the legend. Patient counts are shown on the y-axis. Abbreviations: AML, Acute Myeloid Leukemia; ITD, Internal Tandem Duplication; TKD, Tyrosine Kinase Domain.

Table 2. Distribution of Somatic Mutations Among Patients with AML and Other Hematologic Malignancies

Disease	NPM1	FLT3-ITD	FLT3-TKD	JAK2	RARA
AML	57	7	2	0	0
Other	0	0	0	0	3

AML, Acute Myeloid Leukemia; NPM1, Nucleophosmin 1; FLT3-ITD, Fms-like tyrosine kinase 3 - Internal Tandem Duplication; *FLT3-TKD,* Fms-like tyrosine kinase 3 - Tyrosine Kinase Domain; *JAK2*, Janus Kinase 2 mutation; RARA, Retinoic Acid Receptor Alpha

cases but were absent in MPN and APL. Among AML patients, *FLT3-ITD* and *FLT3-TKD* mutations occurred in 25% and 10%, respectively. The *JAK2* V617F mutation was identified in 90% of MPN cases and was only rarely observed in AML or APL. In contrast, the PML-RARA fusion was detected in 95% of APL cases. These findings confirm well-established genotype–phenotype correlations. A detailed distribution of mutation frequencies by disease type is provided in Table 2, and illustrated graphically in Figure 1.

Patient Demographics and Baseline Features

Among the 100 patients analyzed, 40% were diagnosed with AML, 40% with MPN, and 20% with APL. The sex distribution was balanced, with males and females each accounting for approximately 50% of the cohort. Baseline characteristics, including mutation status and parvovirus B19 detection, are summarized in Table 1.

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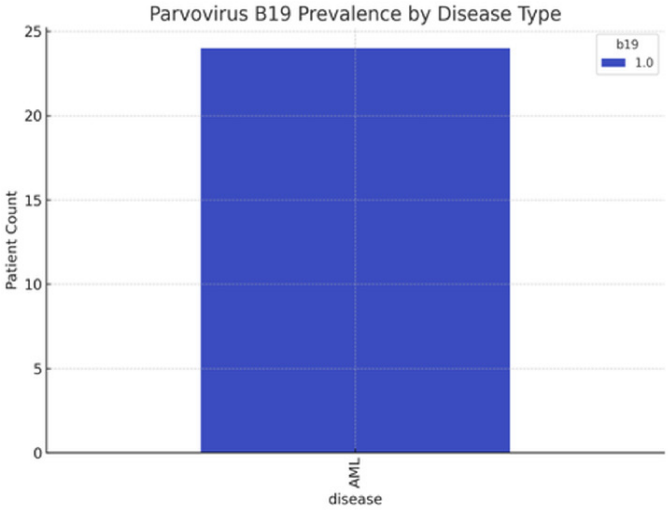

Figure 2. Parvovirus B19 Prevalence by Disease Type.Bar chart showing the number of patients positive for parvovirus B19 DNA among those diagnosed with AML. No cases were detected in other disease categories.Abbreviation: AML—Acute Myeloid Leukemia.

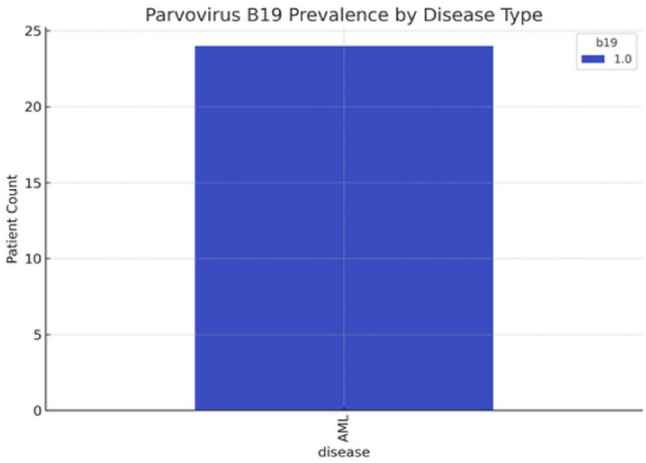

Figure 3. Mutation Co-occurrence Matrix. Heatmap showing the frequency of co-occurring somatic mutations among patients. Higher intensity of color indicates greater co-occurrence. The matrix emphasizes distinct mutation profiles and their relationships, including frequent NPM1 and FLT3-ITD mutations in AML. Abbreviations: ITD, Internal Tandem Duplication; TKD, Tyrosine Kinase Domain.

cases but were absent in MPN and APL. Within AML, *FLT3-ITD* and *FLT3-TKD* mutations occurred in 25% and 10% of patients, respectively. The *JAK2* V617F mutation was present in 90% of MPN cases and was rarely observed in AML or APL. In contrast, the PML-RARA fusion was identified in 95% of APL cases. These findings confirm the expected genotype–phenotype correlations. A detailed distribution of mutation frequencies by disease type is provided in Table 2 and illustrated in Figure 1.

Correlation and Heatmap Findings

The correlation matrix (Figure 5) demonstrated strong positive associations between AML and *NPM1*/FLT3, MPN and *JAK2*, and APL and RARA. Parvovirus B19 infection showed only weak correlations with all other variables ($r < 0.2$), further supporting the absence of a meaningful relationship between viral infection and gene alterations.

Discussion

Our findings reinforce well-established associations between specific mutations and myeloid disease subtypes. As widely documented, *NPM1* and FLT3 mutations were predominantly linked to AML, *JAK2* V617F was characteristic of MPN, and the PML-RARA fusion was nearly universal in APL patients. These associations were statistically significant and consistent with genomic classification frameworks reported in the literature [8–112], as well as the diagnostic criteria outlined in the WHO classification of hematopoietic neoplasms [12]. Persistent parvovirus B19 viremia has been observed in both immunocompetent and immunocompromised individuals, reflecting the virus's ability to evade immune clearance and potentially contribute to chronic marrow suppression [13]. However, in line with previous investigations, our study did not demonstrate a statistically significant association between B19 DNA positivity and specific

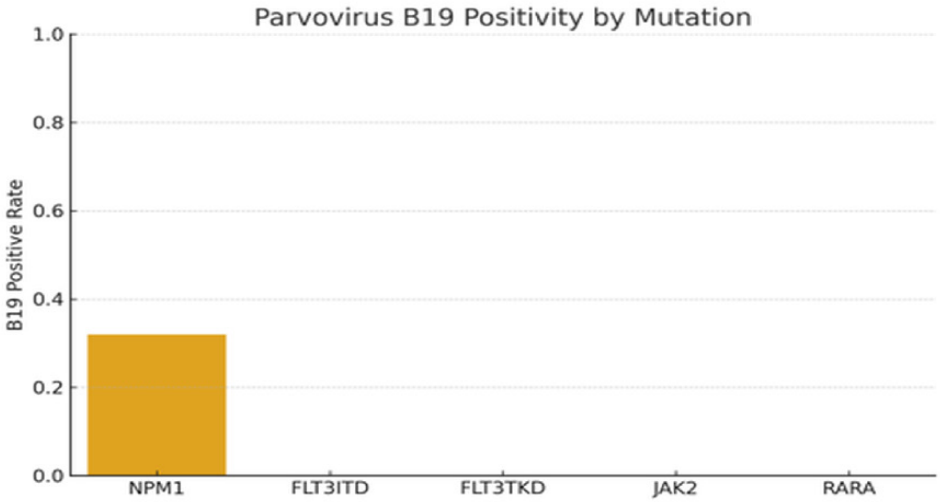

Figure 4. Parvovirus B19 Positivity by Mutation. Bar chart illustrating the rate of parvovirus B19 DNA positivity among patients with various somatic mutations. NPM1-mutated patients show a notable proportion of B19 positivity, while other mutations (*FLT3-ITD, FLT3-TKD, JAK2, RARA*) exhibit minimal or no association.

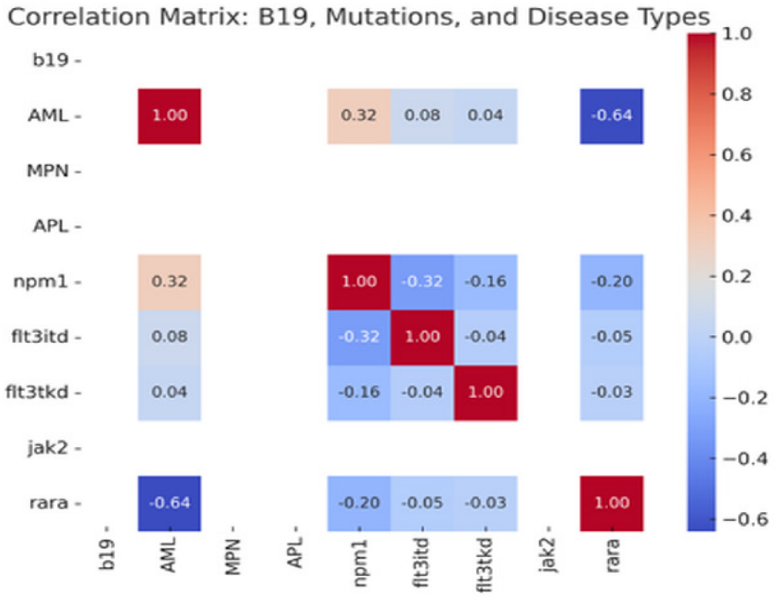

Figure 5. Correlation Matrix of Parvovirus B19, Somatic Mutations, and Disease Types.Heatmap representing Pearson correlation coefficients between parvovirus B19 DNA positivity, key gene mutations (*NPM1, FLT3-ITD, FLT3-TKD, JAK2, RARA*), and hematologic malignancy subtypes (AML, APL, MPN). Strong positive and negative correlations are indicated by red and blue intensities, respectively.

driver mutations in myeloid malignancies. Although B19 has been reported in patients with myelodysplastic syndromes and other hematologic disorders, these studies similarly failed to establish any oncogenic or clonal evolutionary role for the virus [14, 15].

The presence of B19 DNA, especially in the context of immunosuppression or chemotherapy, likely represents dormant or persistent infection rather than active pathogenic involvement [15, 16]. While the virus shows marked tropism for erythroid progenitor cells, it does not appear to influence myeloid-specific mutational pathways [16, 17]. Some reports have hypothesized that chronic B19 infection could contribute to marrow failure or cytopenia through immune-mediated mechanisms, but without consistent molecular links to leukemogenic mutations [18]. Rare case reports have even suggested detection of B19 DNA preceding the development of AML particularly granulocytic sarcoma but these claims remain anecdotal and unsupported by robust evidence [19].

Taken together, these findings indicate that the occasional detection of B19 DNA in patients with myeloid malignancies should be interpreted with caution. Inconsistent associations may reflect peculiarities of host immune responses in leukemia or the sporadic, transient nature of B19 viremia, rather than a causal pathogenetic role.

Algwaiz et al. [20] emphasized the pathophysiological role of parvovirus B19 in anemia and marrow suppression but did not implicate it as a mutation-driven cause of malignancy. Our findings are consistent with this view, supporting the argument that B19's role in myeloid neoplasms is more likely opportunistic and secondary to immunosuppression, rather than causative or mutagenic.

In our cohort, parvovirus B19 showed no significant association with any particular mutation or disease category. Although B19 DNA was detected in 15% of AML cases, 10% of MPN cases, and 5% of APL cases, these differences were not statistically significant. Similarly, no correlation was observed between B19 infection and specific driver mutations. These findings contrast with some prior studies reporting B19 DNA in cerebrospinal fluid or peripheral blood of leukemia patients [20, 21], as well as pediatric studies describing higher B19 prevalence in children with ALL, particularly at diagnosis or during immunosuppressive therapy [22].

Although some publications have linked B19 infection with delayed treatment or exacerbation of anemia in hematologic malignancies [20, 22], our results suggest that in adult myeloid neoplasms, B19 presence is most likely incidental. Given the ubiquity of parvovirus B19 and its high global seroprevalence in adults, viral DNA detected in leukemia patients especially those who are immunosuppressed likely represents latent or persistent infection rather than oncogenic involvement [3, 4, 21].

Persistent viremia has been documented in both immunocompetent and immunocompromised individuals [13], including post-transplant and chemotherapy patients [19]. B19 infections are also known to reactivate under conditions of bone marrow suppression or immune dysfunction [14]. Collectively, the available molecular data do not support a direct oncogenic role for parvovirus B19 in hematologic malignancies [14, 19].

A recently published study in Egypt [20] investigated the prevalence and clinical significance of human parvovirus B19 infection in patients with hematologic malignancies and detected viral DNA in a substantial proportion of cases, particularly in acute leukemias and aplastic anemia. Despite these findings, the authors reported no significant association between B19 infection and either the onset or type of hematologic malignancy. This aligns with our results and reinforces the view that, while B19 infection may act as a co-factor exacerbating

hematologic conditions especially anemia it is unlikely to directly drive leukemogenesis. The geographic and healthcare parallels between Egypt and Iraq further strengthen the value of these regionally comparative observations.

Within the Iraqi literature, our study adds novelty by directly assessing the relationship between parvovirus B19 DNA positivity and somatic mutations (*NPM1*, FLT3, *JAK2*, and PML-RARA) in adult myeloid malignancies. To our knowledge, no previous Iraqi investigations have simultaneously examined these genetic markers alongside B19 detection.

Rahema et al. [23] reported a high prevalence of B19 DNA (50%) among Iraqi AML patients, significantly higher than in healthy donors, and noted associations with persistent anemia and treatment complications. However, their study did not examine genotypic profiles or somatic mutations, limiting conclusions regarding a direct pathogenic role of B19 in leukemogenesis.

Similarly, Ibrahem et al. [24] evaluated pediatric ALL in Basrah and detected B19 IgG seropositivity in 47.5% of cases, a significantly higher rate than in controls. Importantly, they observed a statistical association with the TEL-AML1 fusion gene, suggesting a possible interaction between viral exposure and specific genetic rearrangements in lymphoid, but not myeloid, malignancies.

In a more recent study, Rahema et al. [23[extended their investigation to ALL patients, reporting elevated rates of B19 DNA detection and seropositivity, particularly following chemotherapy. Despite the broader design, this work similarly did not include somatic mutation analysis, instead concentrating on hematologic parameters and treatment-related morbidity.

In contrast, our data demonstrate that B19 DNA presence was not significantly associated with any major driver mutations in AML, APL, or MPN. These findings suggest that, in the myeloid context, detection of B19 DNA is more likely to represent incidental or background viremia particularly in immunocompromised patients rather than indicating a causative oncogenic role. This interpretation is consistent with recent international reports questioning B19's direct involvement in myeloid transformation and instead supporting the hypothesis of opportunistic reactivation in the setting of host immunosuppression or cytopenia.

Study Limitations

This study has several limitations. First, its retrospective nature prevented longitudinal assessment of viral–host interactions over the disease course. Second, the absence of serologic testing for B19-specific IgM/IgG restricted our ability to differentiate between recent and past infections. Third, our mutation analysis relied on a targeted gene panel, which did not capture other recurrent co-mutations relevant to myeloid pathogenesis, such as *DNMT3A, TET2, IDH1,* and *IDH2*. Finally, coding mutations as binary variables limited our ability to evaluate allele burden or clonal dynamics over time.

Future studies could overcome these limitations by integrating longitudinal clinical data with high-throughput sequencing, broader molecular profiling, and periodic monitoring of B19 DNA. Such approaches would provide greater clarity on whether B19 detection correlates with treatment response, immune status, or disease progression.

In conclusion, this study reaffirms the strong associations between key driver mutations and distinct subtypes of myeloid neoplasms. In contrast, no significant association was identified between Parvovirus B19 infection and any specific oncogenic mutation or disease category. Consequently, routine screening for B19 infection in patients with myelodysplastic or myeloproliferative syndromes may be unwarranted, except in cases of unexplained anemia. These findings refine current understanding of virus–cancer interactions and support the interpretation that B19 DNA detection in hematologic malignancies is more likely incidental than causative.

Author Contribution Statement

Anfal M. Khudhair: Conceptualization, data analysis, manuscript drafting and revision. Dunya Jawad Ridha: Molecular testing, data interpretation, manuscript review. Israa Radwan Ali: Manuscript drafting, literature review. All authors have read and approved the final version of the manuscript.

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Scientific Approval and Thesis Status

The study protocol was approved by the Scientific Committee of the Department of Microbiology, College of Medicine, Al-Iraqia University, as part of its research program. This work is not part of a registered student thesis.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request, with appropriate justification.

Study Registration

This research does not qualify as a clinical trial, guideline, or meta-analysis and, therefore, has not been registered in any clinical trial registry or research database.

Ethical Approval and Compliance

This study was approved by the Ethical Approval Committee of the College of Medicine, Al-Iraqia University, Baghdad, Iraq (Approval No. 2023/175/IRM). Eech step associated with individuals as participants in

the study was processed in line with the ethical principles of the appropriate national and institutional boards of the research as well as the 1964 Declaration of Helsinki and its subsequent modifications. Because this was a retrospective study utilizing de-identified lab data, individual informed consent was not necessary. Anonymized data contained no sensitive information, interviews, or Personally Identifiable Information, thus patient confidentiality was strictly upheld.

Conflict of Interest

The authors declare no conflicts of interest related to this work.

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