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Epidemiology and Clinico-Haematological Features among Patients of BCR-ABL-1-Negative Myeloproliferative Neoplasms

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ABSTRACT

OBJECTIVE: The study was conducted to determine the frequency and clinico-haematological patterns of BCR-ABL1-negative MPNs in patients with a presumptive diagnosis in the Pakistani population. Furthermore, the study utilized bioinformatics analysis to map the underlying genetic landscape of MPNs.

METHODOLOGY: This cross-sectional study included 142 BCR-ABL1-negative MPN patients attending the Haematology Department at Jinnah Hospital, Lahore, from March to September 2023. Patients with a positive report of BCR-ABL1 fusion gene or who were transformed from MPN were excluded from this study. PMF, ET and PV were observed in patients based on their frequency and clinico-haematological patterns. Bioinformatics analyses such as disease-gene association and protein-protein interactions (PPI) were performed to understand the underlying genetic landscape of MPNs.

RESULTS: The frequency of various BCR-ABL1-negative MPN types revealed that among 142 patients, the most frequent subtype was PV (n=81; 57.0%), followed by ET (n=42; 29.6%) and PMF (n= 19; 13.4%). Disease-gene association reveals that *JAK2, CALR, ABL1, ASXL1, TET2, MPL, BCR* and *JAK1* are top associated genes with MPNs. PPI interaction shows JAK1 is strongly associated with JAK2, reflecting their role in the JAK-STAT signaling pathway. Similarly, BCR shows association with ABL1, consistent with the formation of the BCR-ABL1 fusion complex.

CONCLUSION: This study identifies PV as the most frequent BCR-ABL1-negative MPN in the studied cohort and highlights the JAK-STAT signaling pathway as the central molecular driver of MPNs.

KEYWORDS: Myeloproliferative neoplasms, BCR-ABL1 Negative, clinico-haematological patterns, Bioinformatics analysis, *JAK2, CALR.*

INTRODUCTION

Myeloproliferative neoplasms (MPNs) are a heterogeneous group of clonal hematopoietic tumours marked by myeloid lineage proliferation with clinical and haematological overlapping features[1]. The World Health Organization (WHO) classification of MPNs is based on molecular and cytogenetic features[2]. The hypercellularity of the bone marrow with efficient haematopoiesis and a rise in the quantity of red blood cells, granulocytes, and platelets in peripheral blood are characteristics of MPNs[3]. Classic MPNs include chronic myeloid leukemia (CML), identified by the BCR-ABL1 fusion gene from translocation of chromosomes 9q34 and 22q11, while BCR-ABL1 negative MPNs, like Polycythemia vera, essential thrombocythemia, and Primary myelofibrosis, are rare cancers with fewer than 6 new cases per 100,000[3].

The annual incidence rates for PV, ET, and PMF ranged between 0.01 to 2.61, 0.21 to 2.27, and 0.22 to 0.99, respectively[4]. Pathogenetic pathways in PV, ET, and PMF include secondary stromal alterations in the spleen and bone marrow as well as clonal myeloproliferation produced from stem cells[5,6]. The molecular discrimination process began in 2005 when several separate teams identified a point mutation in the *Janus kinase 2 (JAK2)* gene (c.1849G>T) of BCR-ABL1 negative MPNs[7]. In addition to *JAK2, several other major genetic mutations involved in the pathogenesis are of calreticulin (CALR) and the thrombopoietin (TPO) receptor (MPL)*.[8] Due to the varying treatment options and prognoses of each type of BCR-ABL negative MPNS, a clear differentiation between them is required, with ET having the best prognosis and PMF having the worst[9]. Despite the growing use of molecular genetics, clinical characteristics, peripheral blood, and bone marrow morphology remain the primary diagnostic tools. Thrombosis, haemorrhage, and leukemic transformation are the most frequent side effects of BCR-ABLl-negative MPNs[10].

The purpose of this study is to distinguish between several disease subtypes among BCR-ABL1-negative myeloproliferative neoplasms that have distinct clinical and morphological disease patterns and to identify the most prevalent clinical pattern and the most commonly occurring type of BCR-ABL1-negative MPNs in Pakistan. BCR-ABL1-negative MPNs are not well documented in Pakistan. Further, bioinformatics analyses, such as disease-gene association and protein-protein interaction (PPI) mapping, were performed to understand the underlying genetic landscape of MPNs. Therefore, from the standpoint of the haematologist, this investigation could aid in identifying the illness load of each type. Furthermore, understanding the underlying genetic landscape of MPNs provides a comprehensive framework for clinicians to move beyond symptom management toward precision medicine.

METHODOLOGY

Study design and sample size

The cross-sectional study was conducted among 142 patients in a tertiary care Hematology Department at Jinnah Hospital, Lahore, Pakistan, from March to September 2023. The sample size of 142 was calculated to estimate a population parameter with a 95% confidence interval and a 5% margin of error to achieve 80% power of the test.

Inclusion and exclusion criteria

The participants were selected after fulfilling the inclusion and exclusion criteria via non-probability consecutive sampling. Patients between the ages of 18 and 70 years old with presumptive myeloproliferative neoplasms (according to the new 2016 WHO classification) for bone marrow biopsy were included in this study. Patients with BCR-ABL1 fusion gene, current treatment, incomplete investigations, and transformation from MPN were excluded from this study.

Data collection procedure

According to the operational definition of MPNs, the primary clinical and hematologic patterns among patients were recorded, along with the frequency of BCR-ABL1-negative myeloproliferative disorders such as polycythaemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Using data stratification, effect modifiers such as age, gender, and duration of illness were observed. All data were recorded on a specially designed demographic performa.

Statistical Analysis

Data were analyzed using SPSS version 20. Quantitative variables were expressed as mean and standard deviation (mean ± SD), while qualitative variables, including gender and clinical features, were presented as frequencies and percentages. $p \leq 0.05$ was considered statistically significant.

Disease-gene association

Disease-gene association analysis was performed to observe genes associated with MPNs. A network of the top 50 genes was constructed using Cytoscape, based on data and Z-scores retrieved from the DISEASES database (https://diseases.jensenlab.org/).

In silico protein-protein interaction

To observe interactions among disease genes, in silico protein-protein interaction (PPI) was performed via the online website STRING (http://www.string-db.org/).

RESULTS

Demographic distribution

To determine the prevalence of various types of BCR-ABL1-negative MPNs in patients with a presumptive diagnosis of MPNs, the study enrolled 142 Pakistani patients who met the selection criteria in the Haematology Department of Jinnah Hospital, Lahore, Pakistan. The mean age of the patients was 47±11.7 years, with 83 (58%) patients falling between the ages of 18 to 50 and 59(42%) patients falling between the ages of 51 to 70 **(Table I)**. The gender distribution reveals that 56 (39%) were female and 86 (61%) were male **(Table I)**. The mean duration of symptoms was 3.10±1.14 days.

Table I: Demographic distribution

Demographic distribution		Number of patients (n=142)	Percentage
Age (years)	18 to 50	83	58%
	51 to 70	59	42%
Gender	Male	86	61%
	Female	56	39%

n= total number of patients, %= percentage

Distribution among types of BCR-ABL1-negative MPNs

The prevalence of various BCR-ABL1-negative MPN types in patients revealed that out of 142 patients with BCR-ABL1-negative MPNs, 19 cases (13.4%) had primary myelofibrosis, 42 cases (29.6%) had essential thrombocythemia, and 81 cases (57.0%) had polycythemia vera **(Figure 1)**.

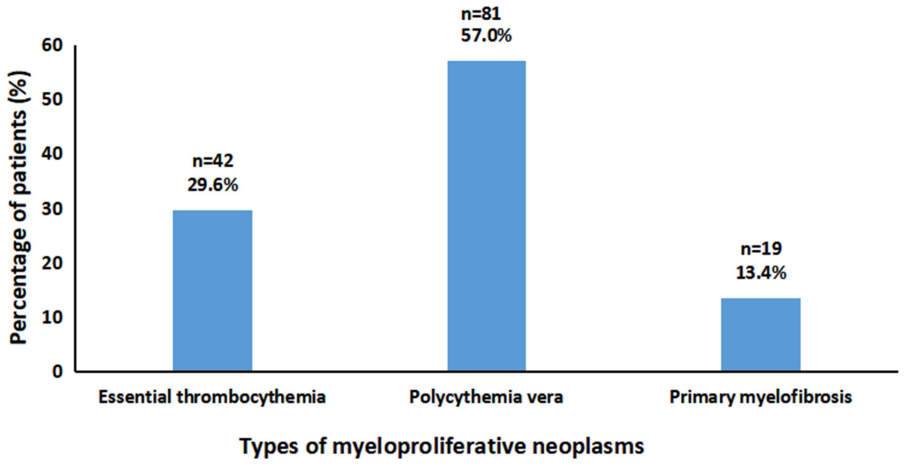

Figure 1: The prevalence of various types of BCR-ABL1-negative myeloproliferative disorders.

Frequency distribution among clinico-haematological patterns

The prevalence of various clinico-haematological patterns in patients with essential thrombocythemia (ET) is as follows: 27 patients (64%) experienced weight loss, 22 patients (52%) experienced pallor, 27 patients (64%) experienced fever, 25 patients (60%) experienced hepatomegaly, 28 patients (67%) experienced bleeding, 32 patients (76%) experienced splenomegaly, 30 patients (71%) experienced thrombocytosis, 22 patients (52%) experienced visual disturbances, and 24 cases (57%) had leukocytosis **(Table I)**.

In patients with polycythemia vera, the frequency of different clinico-haematological patterns is as follows: 49 patients (60%) had weight loss, 53 patients (65%) had pallor, 55 patients (68%) had visual disturbances, 57 patients (70%) had bleeding, 51 patients (63%) had fever, 57 patients (70%) had hepatomegaly, 54 patients (67%) had splenomegaly, 58 patients (72%) experienced thrombocytosis, and 57 patients (70%) had leukocytosis **(Table I)**. The frequency of different clinico-haematological patterns among patients with primary myelofibrosis (PMF) is as follows: 13 patients (68%) had weight loss, 9 patients (47%) had fever, 11 patients (58%) had pallor, 13 patients (68%) had hepatomegaly, 16 patients (84%) had bleeding, 9 patients (47%) had visual disturbances, 11 patients (58%) had thrombocytosis, 12 patients (63%) had splenomegaly, and 15 patients (79%) had leukocytosis **(Table I)**. Transient ischemic attacks (TIAs), strokes, acute myocardial infarctions, and peripheral arterial occlusions were thrombotic complications that occurred in patients with PMF.

Table II: The prevalence of various clinico-haematological patterns among patients of different types of BCR-ABL1-negative myeloproliferative neoplasms

Clinical haematological patterns	Essential thrombocythemia		Polycythemia vera		Primary myelofibrosis	
	n=42	%	n=81	%	n=19	%
Weight loss	27	64	49	60	13	68
Pallor	22	52	53	65	11	58
Visual disturbances	22	52	55	68	9	47
Bleeding	28	67	57	70	16	84
Fever	27	64	51	63	9	47
Splenomegaly	32	76	54	67	12	63
Thrombocytosis	30	71	58	72	11	58
Leukocytosis	24	57	57	70	15	79
Hepatomegaly	25	60	57	70	13	68

n= total number of patients, %= percentage

Distribution of myeloproliferative neoplasm types based on age

The prevalence of various MPN types in patients based on age reveals that out of 42 essential thrombocythemia patients, 24 (57%) were between the age of 18 to 50 years, whereas 18 (43%) were between 51 to 70 years of age. Out of 81 polycythemia vera patients, 50 (62%)

were between the ages of 18 and 50 years, while 31 (38%) were between the ages of 51 and 70 years. Out of 19 primary myelofibrosis patients, 9 (47%) were between the ages of 18 and 50 years, whereas 10 (53%) were between the ages of 51 and 70 years **(Table III)**.

Table III: Prevalence of myeloproliferative neoplasm types stratified by age.

Types of myeloproliferative neoplasms	Age (18 to 50 years)		Age (51 to 70 years)		Total
	No. of patients	%	No. of patients	%	Number of patients
Essential thrombocythemia (n=42)	24	57	18	43	42
Polycythemia vera (n=81)	50	62	31	38	81
Primary myelofibrosis (n=19)	9	47	10	53	19
p value	p<0.05				

n= total number of patients, %= percentage

Distribution of myeloproliferative neoplasm types based on gender

The results of gender distribution among BCR-ABL1-negative MPN patients (n=142) reveal that out of 42 patients with essential thrombocythemia, 30 (71%) were male while 12 (29%) were female. Of 81 patients with polycythemia vera, 42(52%) were male while 39(48%) were female. Out of 19 patients with primary myelofibrosis, 14 (74%) were male while 5 (26%) were female **(Table IV).**

Table IV: Prevalence of various myeloproliferative neoplasm types stratified by gender.

Types of myeloproliferative neoplasms	Male		Female		Total
	No. of patients	%	No. of patients	%	Number of patients
Essential thrombocythemia (n=42)	30	71	12	29	42
Polycythemia vera (n=81)	42	52	39	48	81
Primary myelofibrosis (n=19)	14	74	5	26	19
p value	p<0.05				

n= total number of patients, %= percentage

Disease-gene association

MPN-associated genes were retrieved from the DISEASES database, which integrates data mined from literature. Among them, the top 10 genes are JAK2, CALR, ABL1, ASXL1, TET2, MPL, BCR, JAK1, SRSF2, and THPO, with the highest Z scores, respectively. The interaction network for the top 50 genes is visualized using Cytoscape in **Figure 2.**

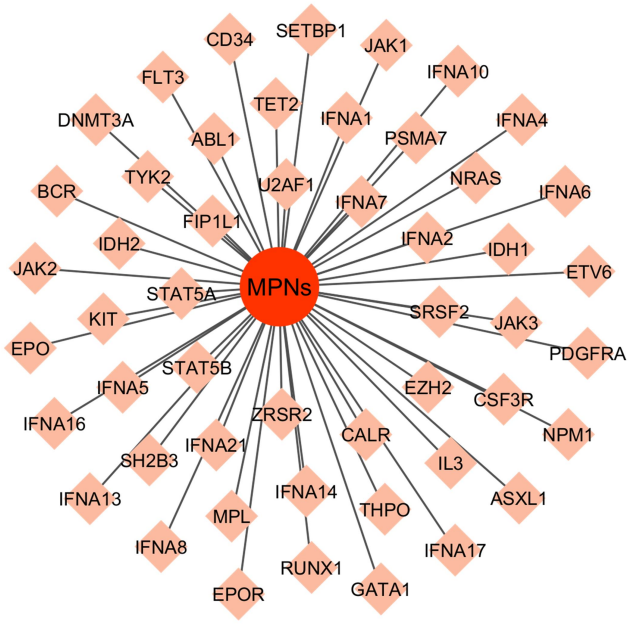

Figure 2: Disease-associated genes created in Cytoscape using data from Diseases. Nodes with light orange or peach colour in diamond are genes associated with MPNs, while nodes with dark orange in circle shape are disease names (MPNs).

PPI interaction among disease-associated proteins

The PPI network shows 49 nodes and 679 edges among the top 50 disease-associated genes with a p-value of < 1.0e-16 and an average local clustering coefficient of 0.786 **(Figure 3)**. PPI networks show very strong interaction among them. JAK1 shows text mining, protein homology, and co-expression with JAK2; similarly, BCR shows text mining, protein homology, and co-expression with ABL1, and ABL1 shows strong interaction with CALR, as shown in **Figure 3.**

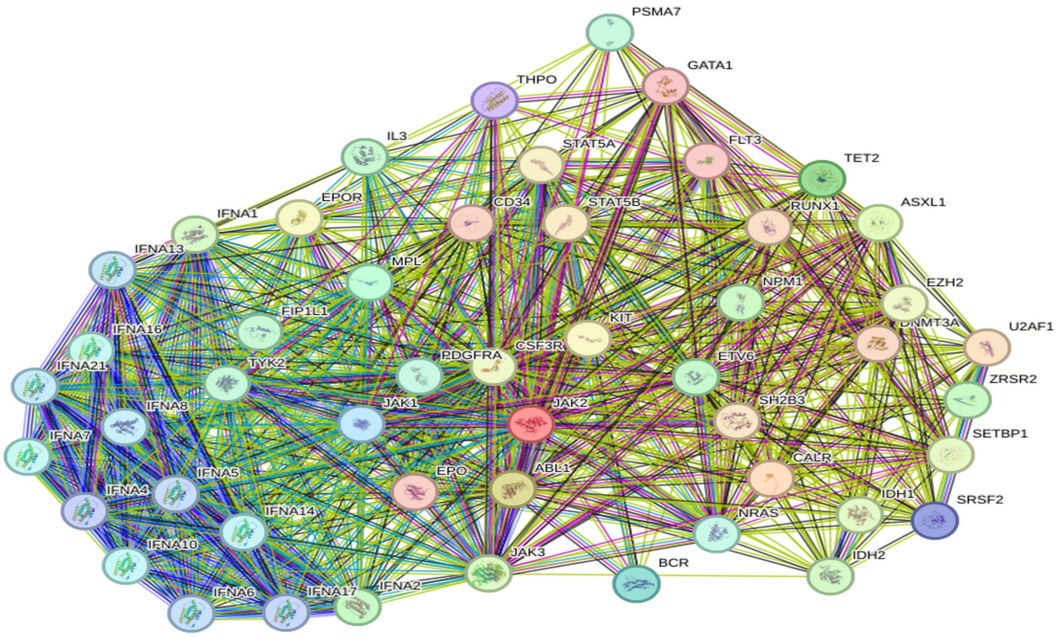

Figure 3: Protein-protein interaction among disease-associated genes by STRING. Nodes represent genes associated with MPNs, while edges show interactions among them.

DISCUSSION

The present study identifies the most prevalent clinical pattern and highest incidence type of BCR-ABL1-negative myeloproliferative neoplasms at Jinnah Hospital, Lahore, Pakistan. Myeloproliferative neoplasms (MPNs) are clonal haematopoietic stem cell disorders that include essential thrombocythemia (ET), polycythaemia vera (PV), and primary myelofibrosis (PMF)[1,2]. Therefore, to identify the clinical pattern and the highest incidence of BCR-ABL1-negative MPNs, 142 patients were selected by following the inclusion and exclusion criteria. The age distribution in our study shows that 58% of patients were between 18 and 50 years of age, whereas 42% were between 51 and 70 years of age, which shows that BCR-ABL1-negative MPNs were more common among patients < 50 years of age; however, this is not consistent with previous studies. As Porto-Soares et al. found, the mean age for all MPNs was 61 years.[11] Similarly, Soro et al. identified 60.8±15 years as the mean age in MPN patients[12]. This may be due to the small sample size in our study. The prevalence of BCR-ABL1-negative MPNs was higher in males (61%) than females (39%) in our study, which is consistent with previous studies[11,12].

Our study found that among BCR-ABL1-negative MPN types, polycythaemia vera (81 patients out of 142) was more prevalent than essential thrombocythemia (42 patients out of 142), which is consistent with a previous study, as they identified polycythaemia vera (61 patients out of 162) as more prevalent than essential thrombocythemia (50 patients out of 162)[12]. Further, our study observed that essential thrombocythemia (42 patients out of 142) was more prevalent than primary myelofibrosis (19 patients out of 142). In contrast, Soro et al. observed almost similar but higher prevalence of Primary myelofibrosis (51 patients out of 162) than essential thrombocythemia (50 patients out of 162).[12] Similarly, Hassan et al. found polycythaemia vera (33 patients out of 89) was more prevalent than essential thrombocythemia (28 patients out of 89) and primary myelofibrosis (28 patients out of 89)[8].

Previous studies found that patients with polycythaemia vera and essential thrombocythemia may present with myeloproliferation symptoms such as pruritus, thrombosis, headaches, erythromelalgia, visual abnormalities, and haemorrhage, or with aberrant laboratory results[13,14]. Conversely, the majority of myelofibrosis patients have constitutional symptoms, early satiety due to significant splenomegaly, anaemia, and crippling fatigue[15]. When clinical characteristics were assessed in our population, our study observed that in essential thrombocythemia, splenomegaly, thrombocytosis, and bleeding were most prevalent. Polycythemia vera showed the highest prevalence of thrombocytosis, leukocytosis, hepatomegaly, and bleeding, while primary myelofibrosis had bleeding. Similar findings were seen in a study at the Armed Forces Institute of Pathology: 66.7% of patients exhibited splenomegaly, 29.16% had hepatomegaly, and only 4.1% had thrombosis in MPN patients[10]. Soro et al. observed splenomegaly and thrombocytosis in MPN patients.[12] Aswad et al. found that the presence of thrombosis in MPN patients is the most frequent consequence in BCR-ABL1-negative MPN that has a major impact on patient death[16]. The results of our study indicate that there is a considerably less harmful form of polycythemia vera, essential thrombocythemia, and Primary myelofibrosis, characterized by fewer occurrences of symptoms and a good response to treatment. None of the individuals experienced the disease's progression to more severe forms like myelofibrosis or myelodysplasia. Further investigation is required into the potential influence of genetic and environmental factors on the milder phenotype of these disorders observed in the Pakistani population.

Our study observed genes associated with MPNs and found that JAK2, CALR, ABL1, ASXL1, TET2, MPL, BCR, JAK1, SRSF2, and THPO are among the top 10 genes, which is consistent with several studies[17,18]. Luque et al. found that *JAK2, CALR,* and *MPL* are the causative events that can initiate MPN disease without cooperating mutations[17]. Similarly,

Zhao et al. reported that *JAK2* mutations are linked to all MPN types, while *CALR and MPL* mutations are associated with ET and PMF[18]. Further, our study observed interaction among the top 50 genes and found *JAK1* is strongly associated with *JAK2* and *BCR* is strongly associated with *ABL1*. O'Sullivan et al. reported that mutations of JAK2 (Janus Kinase), MPL (Myeloproliferative Leukaemia Virus) and CALR (Calreticulin) disorders upregulate JAK-STAT signaling[19]. The JAK-STAT pathway effectively regulates cytokine-dependent gene expression, crucial in normal and abnormal haematopoiesis (blood cell production)[20].

By integrating disease-gene associations and protein-protein interaction (PPI) mapping, this study allows hematologists to move beyond morphology-based diagnosis to a molecularly defined framework for BCR-ABL1-negative MPN subtypes. These bioinformatics insights improve diagnostic accuracy by identifying high-confidence driver mutations (*JAK2, CALR,* and *MPL*)[21] and secondary clonal markers (*ASXL1* and *TET2)*[22] that confirm a malignancy even in "triple-negative" patients or those with a very low mutant allele burden[21,22]. Furthermore, mapping the functional connectivity of these proteins highlights the JAK-STAT signaling axis as the shared pathological engine, enabling clinicians to distinguish between overlapping phenotypes like ET, PV and PMF based on specific genetic signatures rather than clinical symptoms alone.

CONCLUSION

The study summarised that bleeding, fever, splenomegaly, and thrombocytosis were the most common clinical patterns among patients with a presumptive diagnosis of myBCR-ABL1-negative. Further, our study shows higher cases of PV, followed by ET and Primary myelofibrosis. This study identifies the most prevalent clinical pattern and highest incidence type of BCR-ABL1-negative myeloproliferative neoplasms, which was the main significance of this study. Bioinformatics analysis reveals functional connectivity between JAK2, CALR, and MPL proteins, identifying the JAK-STAT signalling pathway as a central driver of MPN pathogenesis. These findings are significant for improving diagnostic accuracy, predicting patient prognosis, and guiding the development of more targeted treatments.

Limitations

The sample size of the study was limited, which may impact the generalizability of the results. Future studies should be done with a larger cohort.

Ethical approval: Allama Iqbal Medical College/Jinnah Hospital, Lahore, Pakistan ERC approval letter No. ERB139/5/20-02-2023/S1 ERB.
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Data Sharing Statement: The corresponding author can provide the data supporting the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Zahid ZUN: Concept and design of the study, conducted experiments, wrote the original draft, and finalized the manuscript.
Fatima S: Helped coordinate and analyze testing, and contributed to the literature review.
Ayaz Q: Formal analysis, *in silico analysis, drafted the results section of the manuscript, and provided* resources for research.
Khan AA: Assisted in patient recruitment and helped in statistical analysis.
Ijaz M: Helped with experimentation.
Rashid Z: Helped in reference and manuscript formatting.

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