RESEARCH ARTICLE

DOI: 10.4274/tjh.galenos.2024.2023.0479
Turk J Hematol 2024;41:1-8

Disseminated Intravascular Coagulation in Acute Promyelocytic Leukemia Patients: A Retrospective Analysis of Outcomes and Healthcare Burden in US Hospitals

Akut Promyelositik Lösemi Hastalarında Yaygın Damariçi Pıhtılaşma: ABD Hastanelerindeki Sonuçların ve Sağlık Hizmeti Yükünün Geriye Dönük Analizi

Rushin Patel[1], Darshil Patel[2], Mrunal Patel[3], Jessica Ohemeng-Dapaah[4], Afoma Onyechi[4], Zalak Patel[5], Chieh Yang[5], Safia Shaikh[6]

[1]*Community Hospital of San Bernardino, Department of Internal Medicine, San Bernardino, USA*
[2]*Rush University, Graduate College, Clinical Research Program, Chicago, USA*
[3]*Trumbull Regional Medical Center, Department of Internal Medicine, Warren, USA*
[4]*SSM Health St. Mary's Hospital, Department of Internal Medicine, St. Louis, USA*
[5]*University of California-Riverside, Department of Internal Medicine, Riverside, USA*
[6]*Washington University, Department of Internal Medicine, St. Louis, USA*

Abstract

Objective: Acute promyelocytic leukemia (APL) is associated with an elevated risk of developing disseminated intravascular coagulation (DIC). The purpose of this study was to assess the outcomes of hospitalizations related to DIC in APL and their impact on healthcare.

Materials and Methods: This study entailed a cross-sectional and retrospective analysis of the US National Inpatient Sample database. We identified adults with APL and categorized them into groups of patients with and without DIC. Our focus areas included in-hospital mortality, length of stay, charges, and complications associated with DIC. Unadjusted odds ratios/coefficients were computed in univariate analysis, followed by adjusted odds ratios (aOR)/coefficients from multivariate analysis that accounted for confounding factors.

Results: Our analysis revealed that APL patients with DIC had a substantially higher aOR for mortality (aOR: 6.68, 95% confidence interval [CI]: 4.76-9.37, p<0.001) and a prolonged length of stay (coefficient: 10.28 days, 95% CI: 8.48-12.09, p<0.001) accompanied by notably elevated total hospital charges (coefficient: $215,512 [95% CI: 177,368-253,656], p<0.001), thereby emphasizing the reality of extended medical care and economic burden. The presence of DIC was associated with increased odds of sepsis, vasopressor support, pneumonia, acute respiratory failure, intubation/mechanical ventilation, and acute kidney injury, reflecting heightened vulnerability to these complications. Patients with DIC demonstrated significantly higher odds ratios for major bleeding, intracranial hemorrhage, gastrointestinal bleeding, red blood cell transfusion, platelet

Öz

Amaç: Akut promyelositik lösemi (APL) yaygın damariçi pıhtılaşma (YDP) gelişim riskinin artışıyla ilişkilidir. Bu çalışmanın amacı APL'de YDP ile ilgili hastane yatışlarının sonuçlarını ve sağlık hizmetleri üzerine etkisini incelemektir.

Gereç ve Yöntemler: Bu çalışma ABD Ulusal Yatan Hasta Örnek veritabanının kesitsel ve geriye dönük bir analizini içermektedir. APL tanılı erişkinleri belirledik ve YDP'si olanlar ve olmayanlar olarak kategorize ettik. Odaklandığımız alanlar hastane mortalitesi, yatış süresi, maliyet ve YDP ile ilişkili komplikasyonlardı. Düzeltilmemiş tahmini rölatif risk oranları (RRO)/katsayılar tek değişkenli analizde hesaplanmış ardından karıştırıcı faktörleri hesaba katan çok değişkenli analizden düzeltilmiş RRO (dRRO)/katsayıları elde edilmiştir.

Bulgular: Analizimiz, YDP'li APL hastalarının mortalite için belirgin şekilde daha yüksek bir dRRO'na sahip olduğunu ortaya koydu (dRRO: 6,68, %95 güven aralığı [GA]: 4,76-9,37, p<0,001). Hastanede kalış süresi belirgin bir şekilde uzamıştı (katsayı: 10,28 gün, %95 GA: 8,48-12,09, p<0,001). Bu durum toplam hastane masraflarını dikkate değer şekilde artırmaktaydı (katsayı: 215,512 $ [95% GA: 177,368-253,656], p<0,001). Bu sonuçlar uzun süreli tıbbi bakımın ve ekonomik yükün gerçekliğini vurgulamaktadır. YDP'li hastalar majör kanama, intrakraniyal kanama, gastrointestinal kanama, kırmızı kan hücresi transfüzyonu, trombosit transfüzyonu, taze donmuş plazma transfüzyonu ve kriyopresipitat transfüzyonu için anlamlı derecede daha yüksek RR oranları göstermiş ve bu da YDP'nin oluşturduğu belirgin hematolojik riskleri işaret etmiştir.

Address for Correspondence/Yazışma Adresi: Rushin Patel, M.D., Community Hospital of San Bernardino, Department of Internal Medicine, San Bernardino, USA
Phone : +1-314-586-2059
E-mail : rushinpateldr@gmail.com ORCID: orcid.org/0000-0002-4854-7414

Received/Geliş tarihi: December 22, 2023
Accepted/Kabul tarihi: February 19, 2024

Abstract

transfusion, fresh frozen plasma transfusion, and cryoprecipitate transfusion, highlighting the pronounced hematological risks posed by DIC.

Conclusion: This study has revealed the significant associations between DIC in APL and various outcomes, underscoring the clinical and economic implications of these conditions. The hematological risks further increase patients' vulnerability to bleeding events and the need for transfusions.

Keywords: Acute promyelocytic leukemia, Disseminated intravascular coagulation, In-hospital mortality, Complications, Length of stay, Charges

Öz

Sonuç: Bu çalışma, APL'de YDP ile çeşitli sonuçlar arasındaki önemli ilişkileri ortaya koymuş ve bu durumun klinik ve ekonomik etkilerinin altını çizmiştir. Hematolojik riskler, hastaların kanamalara karşı hassasiyetini ve transfüzyon ihtiyaçlarını daha da artırmaktadır.

Anahtar Sözcükler: Akut promiyelositik lösemi, Yaygın damar içi pıhtılaşma, Hastane içi mortalite, Komplikasyonlar, Kalış süresi, Ücretlendirme

Introduction

Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia that is physiologically unique from other subtypes. It is distinguished by aberrant proliferation of promyelocytes and has a yearly incidence of 600-800 cases in the United States [1]. It is rare in children under the age of 10, but its prevalence rises during adolescence, peaks in early adulthood, and then remains stable, followed by a decline after 60 years [2]. It presents aggressively and has a complicated coagulopathy that causes bleeding or thrombosis before or during treatment. The clinical symptoms and distinctive morphologic abnormalities of Auer rods on peripheral smears establish APL as a diagnosis.

The most prevalent type of APL is caused by a specific translocation involving the retinoic acid receptors alpha gene (*RARα*) on chromosome 17 and the promyelocytic leukemia (*PML*) gene on chromosome 15 t(15;17)(q22;q12), which results in the formation of the *PML-RARα* fusion gene, thereby leading to clonal promyelocytic expansion [2]. Although it is unclear how this translocation affects leukemogenesis, there is evidence that *PML-RARα* hinders terminal differentiation and subsequently results in the apoptosis of promyelocytes [3].

The most severe clinical manifestation of APL is life-threatening bleeding, primarily caused by increased fibrinolytic-type disseminated intravascular coagulation (DIC). Even though the exact frequency of DIC in APL patients is unknown, a recent epidemiological survey in Taiwan discovered that 90 (77.6%) of 116 APL patients developed overt DIC [4]. The coagulopathy in APL is caused by inappropriate activation of the coagulation cascade by a tissue factor present on the surface of leukemic blasts [5]. This excess release of tissue factor is a common cause of DIC. Another etiology is due to annexin II on the surface of malignant leukocytes, which stimulates the endogenous tissue plasminogen activator and urokinase-type plasminogen activator [5]. This results in hyperfibrinolysis or an excessive breakdown of fibrinogen and occluded fibrin [2]. There is also platelet dysfunction and increased cancer cell cytokine expression (including interleukin [IL]-1β, tumor necrosis factor alpha, and IL-6), which stimulates endogenous tissue factor synthesis, causing the suppression of thrombomodulin and encouraging thrombosis [1,4].

Hemorrhagic episodes due to DIC in cases of APL follow a distinct clinical pattern, and intracranial hemorrhage and pulmonary hemorrhage are the leading cause of death [6,7,8,9]. According to a report from the PETHEMA Group on patients treated in clinical trials with all-trans retinoic acid (ATRA) and idarubicin, 37 of 66 deaths during induction were caused by bleeding, 24 of which were intracranial bleeds and 12 of which were intrapulmonary [7]. According to that study, while most hemorrhagic deaths occurred within the first 10 days following induction, fatal bleeding events persisted until day 23. Excluding patients with subdural hemorrhage, most of the intracranial hemorrhages in the study resulted in death [7].

Induction mortality remains a serious issue and a fundamental cause of treatment failure in managing APL, with hemorrhage contributing to most such cases of early death [1]. The use of ATRA and arsenic trioxide (ATO) in the initial treatment of APL has been one of the most important developments in cancer treatment [8]. This has significantly improved APL outcomes, with over 90% long-term relapse-free survival for individuals who survive the first 30 days after diagnosis. Despite the discovery of highly successful treatment techniques for APL, however, approximately 10% of patients die because of bleeding diathesis in the early course of the disease due to DIC [9]. Our understanding of the prognostic factors related to induction mortality in APL patients has remained extremely limited. Supportive care and other minor diagnostic and therapeutic aspects may play critical roles in patient outcomes, particularly in low socioeconomic settings where early mortality is high and overall survival is poor due to lack of adequate awareness and a multidisciplinary approach to management.

The outcomes of DIC in APL were retrospectively investigated in the present study, thereby offering significant insights into their intricate interaction and their impact on healthcare. This study included a diverse patient population. Hence, the findings may support the development of tailored therapies aimed at reducing mortality and improving the outcomes of APL patients with DIC.

Materials and Methods

This retrospective study employed data extracted from the National Inpatient Sample (NIS) database, which is sponsored by the Agency for Healthcare Research and Quality and constitutes part of the Healthcare Cost and Utilization Project (HCUP) [10]. The NIS database represents an approximate 20% stratified sample of discharges across nearly 1000 US hospitals from all 50 states of the United States. Notably, the NIS database is the largest publicly available all-payer inpatient care database in the United States. This study specifically utilized data from the NIS database spanning the years 2016 to 2019, encompassing hospitalizations from January 1, 2016, to December 31, 2019, and with records of over 24 million hospital stays. Approval from the ethics committee was not needed, as the NIS database that we used contains deidentified data and does not track individuals' information.

Study Population

Using the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10 CM) codes, we identified hospitalizations involving all adult (≥18 years) patients with APL as their principal or secondary diagnosis. We then categorized the patients into two groups as those with DIC and those without DIC.

Outcomes of Interest

Our areas of focus included in-hospital mortality, length of stay, total hospitalization charges, and complications linked with DIC and other associations. For mortality, we utilized the NIS variable "DIED." Length of stay was determined using the NIS variable "LOS." The length of stay for a patient was defined as the total days spent in the hospital from the day of admission to discharge or death. Total hospitalization charges were assessed using the variable "TOTCHG." Additionally, we referred to the relevant ICD-10 codes provided in Supplemental Table 1 to investigate complications and other associations.

Statistical Analysis

All analyses were conducted using appropriate stratifying, clustering, and weighting samples as provided by the regulations of the HCUP [11]. Statistical analysis was performed using STATA version 17 (Stata Corp LLC, College Station, TX, USA). All ICD-10 CM codes used in our study are listed in Supplemental Table 1.

We calculated the odds ratio for dichotomous variables and the coefficient for continuous variables. To create a multivariate analysis model, we included potential confounding variables, which consisted of age, sex, race, income quartile based on zip code, hospital region, hospital teaching status, hospital division, hospital size by beds, insurance status, and the well-established Charlson Comorbidity Index score. The Charlson Comorbidity Index score encompasses conditions such as myocardial infarction, congestive heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes, hemiplegia or paraplegia, chronic kidney disease, diabetes with end-organ damage, solid tumors, leukemia, lymphoma, and AIDS/HIV, all of which are conditions associated with high mortality rates [12].

Initially, we conducted univariate analyses for each of the aforementioned factors to calculate unadjusted odds ratios. Later, in multivariate regression analysis, we used only variables that were associated with the outcomes of interest in univariate regression analysis with a significance level of $p<0.2$. Proportions were compared using the Fisher exact test for categorical variables, and continuous variables were compared using Student's t-test. All p values were two-sided and the significance level was set at $p<0.05$, indicating statistical significance.

Results

Table 1 presents the baseline characteristics of APL hospitalizations in US hospitals. Our study included a total of 2583 hospitalizations of patients with APL, including 2098 hospitalizations without DIC and 485 with DIC. The mean age of the patients without DIC was 53.5 years while the mean age of patients with DIC was 51.4 years, resulting in an overall mean age of 53.1 years. In terms of sex distribution, the sexes were almost equally distributed in both groups and the difference in sex distribution between the groups without and with DIC was not statistically significant. Analyzing the racial distribution, the majority of the patients were white, accounting for 66.0% and 62.0% in the groups with DIC and without DIC, with statistically significant differences observed for both groups. Regarding median household income, the patients were almost equally distributed across all percentile household income categories. An analysis of insurance status revealed that Medicare covered 38.0% of the patients, Medicaid covered 19.1%, private insurance covered 40.0%, and a small percentage of patients

Table 1. Baseline characteristics of acute promyelocytic leukemia hospitalizations.

	Without DIC	With DIC	Total hospitalizations	p
	2098	485	2583	
Mean age (years)	53.5	51.4	53.1	
Sex				0.634
Male	1042 (49.7%)	246 (50.9%)	1289 (49.9%)	
Female	1053 (50.2%)	237 (49.0%)	1291 (50.0%)	
Race				0.037
White	1384 (66.0%)	300 (62.0%)	1686 (65.3%)	
Black	266 (12.7%)	50 (10.4%)	317 (12.3%)	
Hispanic	276 (13.2%)	82 (17.0%)	359 (13.9%)	
Asian or Pacific Islander	63 (3.0%)	18 (3.9%)	82 (3.2%)	
Native American	10 (0.5%)	0 (0%)	10 (0.4%)	
Other	90 (4.3%)	31 (6.5%)	121 (4.7%)	
Median household income				0.025
0^{th} to 25^{th} percentile	618 (29.5%)	110 (22.8%)	728 (28.2%)	
26^{th} to 50^{th} percentile	488 (23.3%)	121 (25.1%)	609 (23.6%)	
51^{st} to 75^{th} percentile	530 (25.3%)	128 (26.5%)	658 (25.5%)	
76^{th} to 100^{th} percentile	455 (21.7%)	123 (25.5%)	578 (22.4%)	
Insurance status				<0.001
Medicare	843 (40.2%)	136 (28.1%)	981 (38.0%)	
Medicaid	394 (18.8%)	98 (20.2%)	493 (19.1%)	
Private insurance	801 (38.2%)	231 (47.7%)	1033 (40.0%)	
No insurance	54 (2.6%)	18 (3.8%)	72 (2.8%)	
Charlson Comorbidity Index score				<0.001
1	0	0	0	
2	767 (36.6%)	229 (47.4%)	997 (38.6%)	
≥3	1328 (63.3%)	254 (52.5%)	1583 (61.3%)	
Admission type				
Non-elective	1795 (85.6%)	450 (92.9%)	2247 (87.0%)	0.151
Elective	302 (14.4%)	33 (7.0%)	335 (13.0%)	
Census division				0.016
New England	90 (4.3%)	24 (5.1%)	116 (4.5%)	
Middle Atlantic	333 (15.9%)	55 (11.5%)	390 (15.1%)	
East North Central	306 (14.6%)	54 (11.1%)	361 (14.0%)	
West North Central	130 (6.2%)	32 (6.6%)	162 (6.3%)	
South Atlantic	434 (20.7%)	102 (21.2%)	537 (20.8%)	
East South Central	153 (7.3%)	30 (6.3%)	183 (7.1%)	
West South Central	211 (10.1%)	55 (11.5%)	268 (10.4%)	
Mountain	113 (5.4%)	24 (5.1%)	136 (5.3%)	
Pacific	312 (14.9%)	102 (21.2%)	415 (16.1%)	
Hospital size by beds				0.041
Small	255 (12.2%)	39 (8.2%)	294 (11.4%)	
Medium	484 (23.1%)	107 (22.2%)	591 (22.9%)	
Large	1355 (64.6%)	336 (69.4%)	1691 (65.5%)	
Hospital location/teaching status				<0.001
Rural	83 (4.0%)	3 (0.6%)	87 (3.4%)	
Urban non-teaching	230 (11.0%)	39 (8.0%)	268 (10.4%)	
Urban teaching	1779 (84.8%)	442 (91.3%)	2223 (86.1%)	

DIC: Disseminated intravascular coagulation.

(2.8%) had no insurance. The majority of patients in both groups were admitted to large hospitals and urban teaching hospitals.

As presented in Table 2, patients who did not have DIC had a lower mortality rate of 4.5% compared to the higher rate of 20.8% among those with DIC. Without DIC, the average length of stay was 13 days, which was shorter than the 25 days observed in the DIC group. Additionally, patients without DIC had lower hospital charges, averaging $166,950, in contrast to the higher mean charge of $396,151 for those with DIC.

Table 3 outlines the risks, outcomes, and interventions linked with DIC in cases of APL.

The adjusted odds ratio (aOR) for mortality was 6.68 (95% confidence interval [CI]: 4.76-9.37, p<0.001), indicating a significant association with DIC and a substantial impact of DIC on patient survival.

The coefficient for length of stay was 10.28 days (95% CI: 8.48-12.09, p<0.001). This implies that patients with DIC experienced significantly more extended hospital stays. The coefficient's magnitude emphasizes this outcome's clinical significance, suggesting that DIC could contribute to prolonged hospitalizations. The coefficient for total hospital charges was $215,512 (95% CI: 177,368-253,656), with a p value of <0.001. The elevated hospital charges highlight the comprehensive impact of this condition on patients and healthcare systems. Moreover, the high aOR values for sepsis and vasopressor support also suggest the high susceptibility of patients with DIC to develop sepsis and require vasopressor support. A statistical difference was observed between patients with and without DIC for respiratory risks including pneumonia, acute respiratory failure, and intubation or mechanical ventilation with respective aOR values of 1.71 (95% CI: 1.25-2.33, p<0.001), 4.27 (95% CI: 3.27-5.59, p<0.001), and 4.46 (95% CI: 3.38-5.89, p<0.001). This demonstrates the high vulnerability of patients with DIC to respiratory complications compared to patients without DIC. The aOR values for major bleeding, intracranial hemorrhage, and gastrointestinal bleeding were 3.86 (95% CI: 2.91-5.10, p<0.001), 5.99 (95% CI: 4.14-8.66, p<0.001), and 1.88

Table 2. Mortality rate, mean length of stay, and mean total hospital charges.

	Without DIC	With DIC
Mortality rate	4.5%	20.8%
Mean length of stay	13 days	25 days
Mean total hospital charges	$166,950	$396,151

DIC: Disseminated intravascular coagulation.

Table 3. Risks, outcomes, and interventions associated with disseminated intravascular coagulation in cases of acute promyelocytic leukemia.

Risks, outcomes, and interventions	Adjusted odds ratio or coefficient	p
Mortality	aOR: 6.68 (95% CI: 4.76-9.37)	**<0.001**
Length of stay (days)	Coefficient: 10.28 (95% CI: 8.48-12.09)	**<0.001**
Total hospital charges ($)	Coefficient: 215,512 (95% CI: 177,368-253,656)	**<0.001**
Sepsis	aOR: 1.84 (95% CI: 1.41-2.39)	**<0.001**
Vasopressor support	aOR: 2.74 (95% CI: 1.44-5.21)	**0.002**
Pneumonia	aOR: 1.71 (95% CI: 1.25-2.33)	**<0.001**
Acute respiratory failure	aOR: 4.27 (95% CI: 3.27-5.59)	**<0.001**
Intubation or mechanical ventilation	aOR: 4.46 (95% CI: 3.38-5.89)	**<0.001**
Clostridioides difficile infection	aOR: 0.63 (95% CI: 0.31-1.28)	0.201
Acute kidney injury	aOR: 2.38 (95% CI: 1.85-3.01)	**<0.001**
Major bleeding	aOR: 3.86 (95% CI: 2.91-5.10)	**<0.001**
Intracranial hemorrhage	aOR: 5.99 (95% CI: 4.14-8.66)	**<0.001**
Gastrointestinal bleeding	aOR: 1.88 (95% CI: 1.27-2.77)	**<0.001**
Pulmonary embolism	aOR: 0.95 (95% CI: 0.50-1.82)	0.870
Red blood cell transfusion need	aOR: 2.80 (95% CI: 2.23-3.52)	**<0.001**
Platelet transfusion need	aOR: 3.78 (95% CI: 2.97-4.82)	**<0.001**
Fresh frozen plasma transfusion need	aOR: 7.32 (95% CI: 4.92-10.87)	**<0.001**
Cryoprecipitate transfusion need	aOR: 10.54 (95% CI: 7.26-15.30)	**<0.001**

aOR: Adjusted odds ratio; CI: confidence interval.

(95% CI: 1.27-2.77, p<0.001), respectively. These results indicate a significant positive association between DIC in APL and the risk of major bleeding. The elevated aOR values underscore the increased susceptibility of these patients to bleeding events. The aOR values for red blood cell transfusion, platelet transfusion, fresh frozen plasma (FFP) transfusion, and cryoprecipitate transfusion were 2.80 (95% CI: 2.23-3.52, p<0.001), 3.78 (95% CI: 2.97-4.82, p<0.001), 7.32 (95% CI: 4.92-10.87, p<0.001), and 10.54 (95% CI: 7.26-15.30, p<0.001), respectively. This suggests significant positive associations between DIC in APL and the need for red blood cell transfusions, platelet transfusions, FFP transfusions, and cryoprecipitate transfusions. The elevated aOR values highlight the heightened likelihood of patients with DIC requiring these transfusions.

Discussion

DIC is life-threatening and causes early morbidity and mortality in patients diagnosed with APL. Our study evaluated the healthcare burdens and outcomes of patients with APL complicated by DIC. Out of the 2583 hospitalizations with APL that we retrospectively assessed, about 19% involved DIC. Although the actual incidence of DIC in APL has not been clearly defined, the incidence of DIC in our study population was much lower compared to previous studies. In Taiwan, an epidemiological study indicated that 90 (77.6%) of 116 APL patients experienced overt DIC [13]. Our investigation did not distinguish between patients who developed DIC before or after chemotherapy induction. The racial distribution in our study population aligned with the patterns previously observed in APL [14]. Patients with DIC have higher odds of developing major life-threatening bleeds, such as intracranial bleeding, as was seen in our study (aOR: 5.99, 95% CI: 4.14-8.66, p<0.001). In a single-center study that evaluated the impact of DIC on induction failure in patients with APL, the leading cause of induction mortality was bleeding, accounting for 66.7% of mortality. The induction mortality rate was 47% in patients with DIC and 11% in patients without DIC [9]. Patients with intracranial hemorrhage tend to have worse outcomes, with higher in-hospital mortality and worse functional outcomes at the time of discharge. In order to reduce secondary brain injury, subsequent therapy focuses on regulating hemostasis, hemodynamics, and intracranial pressure, and most of these cases require observation in an intensive care unit. It is understandable that a substantial number of our cases were managed in metropolitan teaching institutions (84.8% of the DIC-negative and 91.3% of the DIC-positive patients were managed in urban teaching hospitals). In our study population, patients with DIC had more extended hospital stays and higher total hospital charges. Although only a relatively small percentage of our study population (2.8%) lacked insurance, 53.7% of our study population had a household income below the 50th percentile, and the burden of co-pays falls on the patients and society.

The treatment of APL has recently been revolutionized by newer therapies such as ATRA and ATO. Although their exact mechanisms of action remain unclear, ATRA works by various mechanisms, including restoration of autophagy, which serves to degrade the PML-RARa oncoprotein. ATO promotes the autophagy-dependent clearance of the *PML-RARa* gene; synergistically, up to 95% remission may be achieved [15]. Despite these advancements, early death, which is most commonly defined as death within the first 30 days of presentation, remains a major cause of treatment failure. Coagulopathy, leading to intracerebral, gastrointestinal, and pulmonary hemorrhage, is at the forefront of the causes of early death [16,17]. Many clinical trials have failed to include patients with severe coagulopathy/hemorrhage, as they may die even before treatment is initiated. In a Swedish study of 105 APL patients diagnosed between 1997 and 2006, 30 (29%) had early deaths (died within 30 days of diagnosis) and 41% of the early deaths were due to hemorrhage [18]. Our analysis revealed significantly increased odds of mortality from DIC among hospitalized patients with APL (aOR: 6.68, 95% CI: 4.76-9.37, p<0.001). There may be a benefit in further analysis to ascertain whether those deaths were early deaths occurring within 30 days of diagnosis. The management of coagulopathy remains supportive with routine monitoring of platelet count and coagulation parameters and the transfusion of fibrinogen, cryoprecipitate, platelets, and FFP as needed [19]. Our study also revealed statistically higher odds of these patients receiving red blood cell, platelet, FFP, and cryoprecipitate transfusions.

Study Limitations

The NIS database covers inpatient hospitalizations but lacks pre-admission and post-discharge data, preventing long-term follow-up. Given the cross-sectional nature of our data, our findings demonstrate associations rather than causal relationships with the events studied. Moreover, it is essential to acknowledge that our analyses were conducted using retrospective registry data, introducing the possibility of selection bias due to potential selective reporting and the utilization of ICD codes to form the patient cohort. Since the ICD-10 system provides single codes for APL (C924) and DIC (D65), it is not feasible to stratify patients based on APL risk levels (low/intermediate/high) due to the absence of this information in the dataset and the ICD-10 codes. Additionally, crucial details like coagulation panel results, other laboratory values, treatment strategies, and cause of death analyses are absent from our dataset. These considerations are crucial when interpreting our results and their potential implications for clinical practice.

Despite these limitations, our study provides valuable insights into real-world practices for APL patients with DIC. Our goal is to enhance patient outcomes by informing clinical decision-making.

While coding errors and variations exist, the NIS database is widely used and validated. Our study, based on a substantial sample from this database, represents a diverse population across the United States with data from numerous medical centers.

Conclusion

This study has explored the outcomes of DIC in APL, revealing critical insights into their complex relationship. Our analysis revealed significant connections and important clinical implications. These findings could lead to targeted interventions aimed at lowering mortality, improving hospitalization, and easing the financial burdens of APL patients with DIC. Insights into related complications such as sepsis, respiratory issues, and hematological concerns open possibilities for proactive management approaches. This study also paves the way for refining predictive models and personalized treatment plans, enabling healthcare providers to enhance care quality and patient outcomes.

Ethics

Ethics Committee Approval: Approval from the ethics committee was not needed, as the NIS database that we used contains deidentified data and does not track individuals' information.

Informed Consent: Patient consent was not needed as the NIS dataset is deidentified and does not keep information of individuals.

Authorship Contributions

Concept: R.P., D.P.; Design: R.P., D.P.; Data Collection or Processing: R.P., D.P.; Analysis or Interpretation: R.P., D.P., M.P.; Literature Search: M.P., J.O.D., A.O., C.Y., S.S.; Writing: M.P., J.O.D., A.O., Z.P., C.Y., S.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hermsen J, Hambley B. The coagulopathy of acute promyelocytic leukemia: an updated review of pathophysiology, risk stratification, and clinical management. Cancers 2023;15:3477.
2. Choudhry A, DeLoughery TG. Bleeding and thrombosis in acute promyelocytic leukemia. Am J Hematol 2012;87:596-603.
3. Ahmadi T. Case Study: A 26-Year-Old Man With History of Fatigue, Fevers, and Gingival Bleeding. Washington, ASH. Available online at https://www.hematology.org/education/trainees/fellows/case-studies/male-history-fatigue-fevers-gingival-bleeding
4. Ikezoe T. Pathogenesis of disseminated intravascular coagulation in patients with acute promyelocytic leukemia, and its treatment using recombinant human soluble thrombomodulin. Int J Hematol 2014;100:27-37.
5. Ciftciler R, Haznedaroglu IC, Aksu S, Ozcebe O, Sayınalp N, Malkan UY, Buyukasık Y. The factors affecting early death in newly diagnosed APL patients. Open Med (Wars) 2019;14:647-652.
6. Farkas J. Acute Promyelocytic Leukemia (APL). EMCrit Project, 2021. Available online at https://emcrit.org/ibcc/apl/
7. de la Serna J, Montesinos P, Vellenga E, Rayón C, Parody R, León A, Esteve J, Bergua JM, Milone G, Debén G, Rivas C, González M, Tormo M, Díaz-Mediavilla J, González JD, Negri S, Amutio E, Brunet S, Lowenberg B, Sanz MA. Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and idarubicin. Blood 2008;111:3395-3402.
8. Danthala M, Golamari KR, Seshachalam A, Mikkilineni A, Chappidi S, Mekala MB, Elangovan V, Chinnakali P. Walking a tightrope: dosage modifications and treatment outcomes of all-trans-retinoic acid, arsenic trioxide, and daunorubicin for high-risk acute promyelocytic leukemia. JCO Glob Oncol 2020;6:1749-1756.
9. Rahman F, Kabir AL, Khan MR, Aziz A, Baqui MN, Dipta TF, Yunus AB. Disseminated intravascular coagulation in acute promyelocytic leukaemia and its impact on the induction failure: a single centre study. Bangladesh Med Res Counc Bull 2013;39:57-60.
10. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Rockville, AHRQ, 2022. Available online at https://www.ahrq.gov/data/hcup/index.html.
11. Khera R, Angraal S, Couch T, Welsh JW, Nallamothu BK, Girotra S, Chan PS, Krumholz HM. Adherence to methodological standards in research using the national inpatient sample. JAMA 2017;318:2011-2018.
12. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288-1294.
13. Chang H, Kuo MC, Shih LY, Dunn P, Wang PN, Wu JH, Lin TL, Hung YS, Tang TC. Clinical bleeding events and laboratory coagulation profiles in acute promyelocytic leukemia. Eur J Haematol 2012;88:321-328.
14. Matasar MJ, Ritchie EK, Consedine N, Magai C, Neugut AI. Incidence rates of acute promyelocytic leukemia among Hispanics, blacks, Asians, and non-Hispanic whites in the United States. Eur J Cancer Prev 2006;15:367-370.
15. Moosavi MA, Djavaheri-Mergny M. Autophagy: New insights into mechanisms of action and resistance of treatment in acute promyelocytic leukemia. Int J Mol Sci 2019;20:3559.
16. Stahl M, Tallman MS. Acute promyelocytic leukemia (APL): remaining challenges towards a cure for all. Leuk Lymphoma 2019;60:3107-3115.
17. Di Bona E, Avvisati G, Castaman G, Luce Vegna M, De Sanctis V, Rodeghiero F, Mandelli F. Early haemorrhagic morbidity and mortality during remission induction with or without all-trans retinoic acid in acute promyelocytic leukaemia. Br J Haematol 2000;108:689-695.
18. Lehmann S, Ravn A, Carlsson L, Antunovic P, Deneberg S, Möllgård L, Rangert Derolf Å, Stockelberg D, Tidefelt U, Wahlin A, Wennström L. Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish Adult Acute Leukemia Registry. Leukemia 2011;25:1128-1134.
19. Sanz MA, Fenaux P, Tallman MS, Estey EH, Löwenberg B, Naoe T, Lengfelder E, Döhner H, Burnett AK, Chen SJ, Mathews V. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood 2019;133:1630-1643.

Supplemental Table 1. International Classification of Disease, Tenth Revision, Clinical Modification codes used in this study.

Variable	ICD-10 CM/Procedure codes used
Acute promyelocytic leukemia	C924
Disseminated intravascular coagulation	D65
Sepsis	A021, A227, A267, A327, A400, A401, A403, A408, A409, A41, A4101, A4102, A411, A412, A413, A414, A4150, A4151, A4152, A4153, A4159, A4181, A4189, A419, A427, A5486, B377, P360, P3610, P3619, P362, P3630, P3639, P364, P365, P368, P369, R6520, R6521, T8144XA, T8144XD, T8144XS
Vasopressor support	3E030XZ, 3E033XZ, 3E040XZ, 3E043XZ, 3E050XZ, 3E053XZ, 3E060XZ, 3E063XZ
Pneumonia	J180, J181, J182, J188, J189
Acute respiratory failure	J9600, J9601, J9602, J9620, J9621, J9622, J9690, J9691, J9692
Intubation/mechanical ventilation	5A09357, 5A09457, 5A09557, 09HN7BZ, 0CHY7BZ, 0DH57BZ, 0NH17EZ, 5A1935Z, 5A1945Z, 5A1955Z, 0BH07DZ
Clostridioides difficile infection	A047, A0471, A0472
Acute kidney injury	N170, N171, N172, N178, N179
Major bleeding	R58, L7622, K661, I62, I620, I6200, I6201, I6202, I6203, I621, I629, R04, R040, R041, R042, R048, R0481, R0489, R049
Intracranial hemorrhage	I6000, I6001, I6002, I6010, I6011, I6012, I602, I6030, I6031, I6032, I604, I6050, I6051, I6052, I606, I607, I608, I609, I6030, I6030, I610, I611, I612, I613, I614, I615, I616, I618, I619, I6200, I6201, I6202, I6203, I621, I629
Gastrointestinal bleeding	K920, K921, K922, K625, K928, K929, K9281, K9282, K9289, K250, K254, K260, K264, K270, K28, K621
Red blood cell transfusion	30233N0, 30233N1, 30243N0, 30243N1, 30273N1, 30277N1, 30233P0, 30233P1, 30243P0, 30243P1
Platelet transfusion	30233R1, 30243R0, 30243R1, 30273R1, 30277R1
Fresh frozen plasma transfusion	30233L0, 30233L1, 30243L0, 30243L1, 30273L1, 30233K0, 30233K1, 30243K0, 30243K1, 30273K1, 30277L1, 30277K1
Cryoprecipitate transfusion	30233M0, 30233M1, 30243M0, 30243M1, 30273M1, 30277M1, 30233D1, 30243D1
Pulmonary embolism	I26, I260, I2602, I2609, I269, I2692, I2699

ICD-10 CM: International Classification of Disease, Tenth Revision, Clinical Modification.