Percutaneous coronary intervention and in-hospital outcomes in patients with leukemia; a nationwide analysis

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Percutaneous coronary intervention and in-hospital outcomes in patients with leukemia; a nationwide analysis

Short running title: PCI outcomes in leukemia patients

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Abstract:

Objectives: To examine the association between current leukemia diagnosis and in-hospital clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) in the US.

Background: Leukemia is most common hematological malignancy and is associated with an increased risk of thrombotic and bleeding complications in patients undergoing PCI. There are limited data around clinical outcomes of leukemia patients undergoing PCI.

Methods: We used the National Inpatient Sample (NIS) to investigate the outcomes of leukemia patients undergoing PCI between 2004 and 2014. Patients were then subdivided into diagnoses of acute or chronic myeloid leukemia (AML or CML) and acute or chronic lymphoid leukemia (ALL, CLL). Multiple logistic regressions were used to study the association of a leukemia diagnosis with in-hospital outcomes; mortality, bleeding, vascular and cardiac complications, and stroke.

Results: There were 6,561,445 records of patients who underwent PCI during the study time, of which 15,789 patients had a diagnosis of leukemia. The most common leukemia subtype was CLL accounting for 75% of the cohort (n=10,800). After multivariable adjustment, a leukemia diagnosis was associated with significantly increased odds of in-hospital mortality (OR 1.41 (95% CI (1.11-1.79)) and bleeding (OR 1.87 (95% CI 1.56-2.09)), whereas patients with AML had a 5-fold increase of in-hospital mortality (OR 5.38 (95% CI 2.94-9.76)).

Conclusion: Patients with current diagnosis of leukemia are at increased risk of procedure-related complications following PCI. A multi-disciplinary approach is needed amongst interventional cardiologists, oncologists and hematologists to minimize procedural complications and improve outcomes in this high-risk cohort.

Keywords: Leukemia, Percutaneous coronary intervention, clinical outcomes, mortality

Introduction

Percutaneous coronary intervention (PCI) is the most common modality of coronary revascularization, with over 600,000 PCI procedures undertaken annually, at an estimated aggregate cost of $10 billion in the US.(1) Patients undergoing PCI are increasingly elderly, with contemporary registry studies suggesting that at least 75% of patients undergoing PCI have at least one coexisting comorbid condition.(2,3) With advances in the treatment of cancer and improving survival, a cancer diagnosis is increasingly encountered as a comorbid condition in patients undergoing PCI.(4-8)

Hematologic malignancies account for 10% of all new cancer diagnoses in contemporary datasets, with leukemia amongst the most common hematological malignancies with an incidence rate in the United States reported as 13 cases per 100,000 population in 2014.(9) Contemporary data suggests that 2.5% of patients undergoing PCI have a current or prior history of hematological malignancy.(10) Leukemia are a broad spectrum of malignancies occurring because of clonal proliferation of hematopoietic stem cells in the bone marrow. The prevalence of leukemia is generally higher in males, increases with age and approximately one in 70 persons develop leukemia in their lifetime.(11) The four most common subtypes of leukemia are acute lymphoblastic (ALL), acute myelogenous (AML), chronic lymphocytic (CLL), and chronic myelogenous (CML), with different clinical courses and outcomes, particularly in relation to risk of thrombotic and major bleeding complications.

Leukemia-related thrombocytopenia and platelet dysfunction increase the risk of major bleeding complications that are known to be independently associated with a 3-fold increase risk of mortality and major adverse cardiovascular complications in PCI.(12,13) Coagulopathies associated with leukemia may increase the risk of stent thrombosis, (14) known to be associated with increased risk of mortality.(15,16) Furthermore, certain tyrosine kinase

inhibitors used in the treatment of certain types of leukemia such as chronic myeloid leukemia are associated with an increased risk of acute myocardial infarction.(17,18)

Outcomes of patients with leukemia following PCI are limited to isolated case reports,(14,19-22) with no previous literature that has systematically studied the prevalence of different types of leukemia in contemporary cohorts of patients undergoing PCI, their clinical characteristics or associated clinical outcomes, and whether there are differences amongst the different leukemia subtypes. Data from randomized controlled trials in this cohort are lacking, with randomized controlled trials of cardiovascular care and outcomes in patients undergoing PCI excluding patients with active malignancy and treatment.

The Nationwide Inpatient Sample offers an opportunity to evaluate the association between a leukemia diagnosis and outcomes in the "real-world" setting of a large, contemporary cohort of over 6 million U.S. patients undergoing PCI. In this analysis, we examine temporal trends, clinical and procedural characteristics, and clinical outcomes stratified by both the presence of a leukemia diagnosis and type over a 10-year period.

Materials and Methods

Data source

The National Inpatient Sample (NIS), is the largest publicly available all-payer database of hospitalized patients in the United States and is sponsored by the Agency for Healthcare Research and Quality (AHRQ) as a part of the Healthcare Cost and Utilization Project.(23) It includes anonymized data on primary and secondary discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset was designed to approximate 20% stratified sample of United States community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population.

Study design

All individuals who had undergone a PCI (both balloon angioplasty and with a stent) for both elective and ACS indications between January 2004 and December 2014 were ascertained by identifying all eligible discharges with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes of either 00.66, 36.06 or 36.07 Before a revision of the codes in 2005 the codes 36.01, 36.02 and 36.05*)* were used and so these codes were also included when identifying procedures in discharges from 2004 and 2005 as we have previously described. (10)

Records were eligible for inclusion if the discharge record showed that a PCI procedure had been performed during the hospitalization and the patient was over the age of 18. Information of patient demographics is recorded for each hospital discharge including data regarding age, gender, race, admission type (elective/emergent), admission day (weekday/weekend), median household income according to ZIP code, the expected primary payer and patient comorbidities extracted using the Elixhauser Comorbidity Software.(24) Each discharge record had information on up to 30 diagnoses that the patient had been given, and it was these diagnosis codes that were used to identify whether the patient had a diagnosis of cardiogenic shock, ST-elevated myocardial infarction or non-ST-elevated myocardial infarction during hospitalization. These diagnosis codes were also used to identify other patient comorbidities including smoking, hypercholesterolemia, and historical patient information.

Finally, information about the PCI procedure was determined from the procedure codes, including whether the PCI was multi-vessel, the type of stent used (bare metal, drug-eluting) and whether it involved bifurcation stenting. The use of an assist device (such as an intra-aortic balloon pump) was also recorded.

We used ICD-9 codes of 204.xx (lymphoid leukemia), 205.xx (myeloid leukemia, 206.xx (monocytic leukemia), 207.xx (other specified leukemia) and 208.xx (leukemia of unspecified

cell type) to identify records with diagnosis of leukemia. The leukemia diagnosis was subdivided to consider AML, CML, ALL and CLL subtypes.

Clinical Outcomes

The main outcomes chosen included: in-hospital mortality and complications, including bleeding, vascular complications, cardiac complications or a post-operative stroke.

Procedural complications were also identified using ICD-9-CM codes and patient safety indicators including: post-procedural hemorrhage requiring transfusion, vascular injuries, cardiac complications including iatrogenic and pericardial complications, whether an emergency coronary artery bypass grafting or bailout and a post-procedural stroke or transient ischemic attack. Finally, bleeding complications were identified, including gastrointestinal, retroperitoneal, intracranial, intracerebral hemorrhage, unspecified hemorrhage, and whether a blood transfusion was required (Supplemental Table 1).

Statistical analysis

Statistical analysis was performed on STATA/MP version 14.0. Continuous variables are presented as a median and interquartile range, due to skewed data, and categorical data are presented as number and percentage. Observations with missing data were removed. For all analyses, the survey estimation commands were used (by using the svy prefix in analyses conducted in Stata), this followed the recommendations from AHRQ for analysis of survey data to account for the complex survey design of the NIS database. The use of sampling weights is required because the design of the study means that different observations may have different probabilities of selection. Due to records being sampled by hospitals rather than individuals, clustering of records within hospitals was taken into account in the survey estimation. This was done by defining each hospital to be the primary sampling unit. For calculation of national

estimates and correct variances, sampling weights for each individual discharge that were provided by the AHRQ were used.

Multivariable logistic regression analyses were conducted firstly to investigate the association between a diagnosis of leukemia, compared to those records with no leukemia diagnosis on in-hospital (a) mortality, (b) individual defined complications (c) composite of the considered complications. Secondly, the association between the 4 specific subtypes of leukemia (AML, CML, ALL, CLL) and in-hospital mortality and complications were considered. In order to assess the impact of the leukemia diagnosis, all models were adjusted for potential confounders. These included age, gender, median income, expected payer, elective admission, primary diagnosis of MI, diagnosis of ST-elevation myocardial infarction (STEMI)/non ST-elevation myocardial infarction (NSTEMI), diagnosis, diagnosis of shock, use of an assist device or IABP, the type of stent used, multi-vessel PCI, year of hospitalization, Elixhauser comorbidities, smoking status, and previous MI, PCI, CABG or stroke.

Results

A total of 7,121,387 PCI procedures for elective and ACS indications were undertaken between 2004–2014. Discharges with less than 10% missing data for included outcomes as well as covariates including age and gender were excluded so that 6,561,445 procedures were included in the final analysis. In total, approximately 7% (n=105,007) of the procedures were removed due to missing data, Supplemental figure 1.

Table 1 shows the patient demographics of included records stratified by whether the patient has leukemia or not. A total of 15,789 patients (0.24% of the cohort) with a current history of leukemia diagnosis were identified. Patients who have leukemia were on average older (median age 73 vs 65), more likely to be male (73% vs 66%) and less likely to be admitted for an elective procedure (23% vs 27%). Patients were also more likely to receive a BMS in

the leukemia group (30.3% vs 22.0%), although over time the use of bare metal stents reduced within both groups (Supplemental figure 2). Leukemia patients were also more likely to be diagnosed with NSTEMI (28% vs 23%). After considering the patient demographics stratified by leukemia diagnosis, subtypes of leukemia type were identified, AML, CML, ALL and CLL. There were 1481 records for which none of these subtypes were applicable, and were not considered in the next part of the analysis. Table 2 shows the patient demographics of included records for each of the subtypes. The most common subtype was CLL with 10,800 patients identified accounting for 68% of the cohort. There was up to a decade difference in the median age ranges of patients in each of the group (64–74 years). Patients with ALL were the most likely to be admitted for an elective procedure (25%) with AML patients least likely to be admitted for an elective procedure (19%).

Clinical outcomes

Patients with leukemia had higher rates of in-hospital mortality, bleeding complications, vascular complications and the composite of all complications compared to patients without leukemia (Table 3). Multivariable analyses were conducted to assess the impact of leukemia. There was a 40% increase in the odds of mortality for patients with leukemia compared to those without (1.41 OR (95% CI 1.11-1.79)) (Table 4, Figure 1). Significant increases were also seen for any complication (1.21 OR (95% CI 1.09-1.34)) and bleeding complications (1.81 OR (95% CI 1.56-2.09)).

Table 5 shows the complication rate and in-hospital mortality for the subtypes of leukemia. Mortality was highest in patients with AML (12.2%) followed next by ALL (4.6%). Complication rates were mostly higher in patients with an acute form of either lymphoid or myeloid leukemia. Multivariable analyses were conducted to assess the effect of the subtypes of leukemia. Patients with AML had a 5-fold increase in in-hospital mortality than patients with no leukemia (5.38 OR (95% CI 2.94-9.76)) (Figure 2). There were statistically significant

increases in the odds of any complications in patients with AML (2.65 OR (95% CI 1.84-3.82)) and ALL (2.24 OR (95% CI 1.08-4.66)). There were also significant increases in the odds of bleeding complications for all 4 subtypes of leukemia (Table 6). Further investigation into individual types of bleeding is given in Supplemental Table 2.

Discussion

Data on PCI outcomes or complications in patients with leukemia is limited, as these patients are routinely excluded from the majority of PCI clinical trials.(4) To our knowledge, this is the first study to specifically address this population of oncologic patients undergoing coronary revascularization. Our analysis suggests that patients with leukemia are relatively uncommon in contemporary PCI practice representing 0.3% of the caseload. We show that a diagnosis of leukemia is associated with adverse clinical outcomes following PCI, particularly AML where in-hospital crude rates of mortality and bleeding were 12% and 22%, respectively. Following adjustment for baseline covariates, the adverse outcomes associated with a diagnosis of leukemia were mainly observed in those patients with acute forms of leukemia (AML and ALL).

The management of leukemia differs according to type, with each form associated with different complications, comorbidities, and outcomes. There have been major therapeutic developments in the field of Hematology-Oncology that have increased leukemia patients' lifespan, meaning that these patients will be increasingly encountered in contemporary PCI. (4,25-27) In support of this, we have observed a steady increase in the prevalence of patients undergoing PCI with a diagnosis of leukemia between the years 2004-2014. This trend is likely to have been driven by the increase in survival in patients with CLL (that account for 75% of patients in this series), with the inception of treatment with imatinib, which has decreased disease mortality from 10-20% to 1-2%.(28) Our analysis provides an overview of patient characteristics/comorbidities, disease burden (single, multivessel disease), type of stent (BMS

vs. DES), complication rate and procedure-related outcomes in a national leukemic cohort population as well as to specific leukemia subtypes (AML, CML, ALL and CLL). Patients with leukemia were on average older (median age 73 vs 65) mainly driven by the larger number of CLL patients (older age at diagnosis and better survivorship). As expected, in patients with leukemia we observe an increased prevalence of anemia (2-fold), coagulopathy (5-fold) as well as an increase in renal dysfunction (15.5% vs 9.6%), that may in part be attributed to the nephrotoxicity of some chemotherapeutic agents used to treat leukemia. The highest rates of in-hospital mortality were noted with AML (12.2%) followed by ALL (4.6%), as well as the highest bleeding complications (AML 22%, ALL 18.2%). It is not surprising that patients with AML and ALL had higher in-hospital mortality as these patients tend to be sicker and disease-specific treatments can be associated with immunosuppression, cardiotoxicity, profound thrombocytopenia, bleeding diathesis or hypercoagulable states (i.e. acute promyelocytic leukemia (APL)).(29,30) Furthermore, we noted more post-procedural stroke with AML (4.7%).

ALL was relatively uncommon in this PCI population (210 subjects), as patients diagnosed with ALL tend to be young with a low burden of coronary disease. The ALL population had the highest prevalence of STEMI (47.7%), shock (9.1%), use of assist device or IABP (4.6%) with single vessel stenting (77.3%). Combined with the high percentage of CHF (15.9%) we can identify at least 3 plausible explanations as individual elements or multifactorial. The first one is the high incidence of STEMI and associated acuity; possibly some of these cases could be related to leukemic blast clot, or chloroma causing ST-segment elevation myocardial infarction.(31) The second etiology of this ventricular decompensation can derive from the LV involvement by malignant lymphocytic neoplasms that have been reported in 8.7% to 37% of autopsy cases involving lymphoma or leukemia. (32-34) This has been better described in CLL populations, where leukemic infiltrates were reportedly present

in the heart (64%) with the association of fibrosis-leukemic infiltration present in the heart (44%).(35) The third possible explanation may reside in the approximately 10% of cancer patients that are diagnosed clinically with an NSTEMI, that have stress-induced cardiomyopathy (Takotsubo syndrome),(36,37) with the most common complication being cardiogenic shock requiring inotropic agents (20%).(36) Takotusbo syndrome can go undiagnosed if cardiac imaging is not performed prior to/following invasive angiography.

Patients with chronic leukemia also had a higher proportion of procedure-related complications and bleeding when compared with patients without leukemia. For CML, treatment with nilotinib and ponatinib have shown an increase in vascular events.(28) Similarly, ibrutinib which is used in the treatment of CLL is known to be associated with bleeding and atrial fibrillation as side effects.(38) Patients with leukemia present challenges both during and after PCI due to disease and treatment-related issues regarding both hemostasis and bleeding risk as well as an increased risk of thrombosis, which is particularly of significance in acute leukemia. Depending on the circumstances, judicious deferment, use of the transradial access site to minimize bleeding complications and intra-coronary imaging may help decrease these complications.(39)

In all patients with leukemia, due to the higher risks associated with the procedure as well as the potential for complications with antiplatelet agents in patients in whom the platelet counts may already be compromised, the decision to proceed with PCI should be made by an interdisciplinary team that should include oncology, cardiology/interventional cardiology, internal medicine as well as other consultative services to balance procedural risks versus patient benefit where possible. Judicious deferment of PCI can also be considered particularly in elective cases when a higher rate of procedure-related complications is anticipated. From an operator perspective, the number of procedures and percentage of drug-eluting stents (DES) implanted in patients with leukemia has increased, suggesting the comfort level to implant them

is changing, particularly with the introduction of DES platforms that require shorter durations of DAPT into clinical practice.(40) The use of radial access,(13,41) introduction of thinner strut and polymer free platforms that require shorter duration of DAPT, and the use of intravascular imaging (intravascular ultrasound IVUS and Optical Coherence Tomography (OCT)) to optimize PCI results has enabled the interventional cardio-oncology programs to have acceptable rates of complications in this challenging group of patients.(39,42) Furthermore, the use of less potent anticoagulation, lower rates of Glycoprotein IIb/IIIa and less potent antiplatelet therapy are avoidance strategies in patients with high bleeding risk.(43,44)

Study limitations

Our study findings need to be interpreted in light of our study design since analyses of large databases have certain inherent limitations. Although the NIS database contained variables of interest, additional data (platelet count, antiplatelet regimen, disease staging – advanced cancer) are not routinely collected and may provide additional information to better stratify risk, case complexity, and immediate peri-procedural outcomes. The outcome measures available from the NIS relate only to in-hospital outcomes and do not capture longer-term follow-up of mortality and other adverse events that are important to understand in patients with leukemia such as reinfarction. While there is a considerable granular data relating to the PCI admission (e.g. STEMI on presentation vs. during hospitalization), full procedural details are not recorded in the NIS, therefore, limiting insights into differences in angiographic findings (e.g. target lesion or vessel revascularization and stent thrombosis), PCI procedural techniques (e.g. femoral vs. radial access), and clinical outcomes. Additionally, no pharmacological information is recorded on NIS preventing the further assessment of antiplatelet and anticoagulant choices as well as disparities in the use of guideline-directed evidence-based therapies in patients with leukemia, or the use of cancer drug therapies, many

of which have cardiotoxic actions themselves, which may contribute to the adverse outcomes. Furthermore, the NIS dataset does not capture platelet or hemoglobin counts, which may influence antiplatelet and stent choice. The higher rate of BMS use in the leukemia cohort may reflect a higher prevalence of anemia and thrombocytopenia in this group of patients that are known to increase the risk of major bleeding complications. Leukemia is relatively rare, as only 0.3% of patients undergoing PCI had a diagnosis, this leads to comparisons of small numbers of patients with a large group of patients which may provide less robust comparisons. The NIS dataset only captures PCI procedures undertaken as inpatient procedures, and our analysis provides no insight into the prevalence and outcomes of leukemia in PCI procedures undertaken as outpatient procedures. Finally, in keeping with all observational registry work, the possibility of unmeasured or unrecognized confounders may contribute to the adverse outcomes, although capture of a wide range of comorbid conditions in the NIS may help to mitigate this

The present study was a national cohort study, encompassing simple and complex lesions, tertiary and non-tertiary care settings, and immediate peri-procedure follow-up. The implications of our findings underscore the need to enroll patients with leukemia in prospective registries for short and long-term outcomes and suggests that there will be a need for additional resources to care for this growing group of overall older adults with leukemia. The interventional cardiologist should develop some understanding of cardio-oncology care for this small, but an increasing number of patients that carry the burden of malignancy, atherosclerotic disease and have an understanding of the increased morbidity and mortality associated with the bleeding and thrombotic risk of the disease as well as the therapies.

Conclusion

This is the first study of outcomes post-PCI in a cohort of patients admitted with a diagnosis of leukemia. Patients with leukemia, particularly acute forms of leukemia are at a greater risk of procedure-related complications after PCI compared to patients without leukaemia, and will require a complex multi-disciplinary approach to balancing the risks associated with the procedure to the benefits. As the survival rates of patients with leukemia continue to increase, they will be increasingly encountered in contemporary PCI. Specific cardio-oncology registries or adding cancer-related data to current national and international registries will be needed to provide new insight and improve the care of this high-risk population group.

Disclosures:

All authors declare that there is no competing conflict of interest relevant to this study or any content presented in the manuscript.

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Figure Legends:

Figure 1. Adjusted odds ratio (OR) of adverse events in leukemia

Legend: *Reference group; CI: confidence interval; § non-significant; † p<0.001

Figure 2. Adjusted odds ratio (OR) of adverse events according to leukemia subtype

Legend: *Reference group; CI: confidence interval; § non-significant; † p<0.001; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; ALL: acute lymphoid leukemia; CML: chronic lymphoid leukemia

Table 1: Patient demographics and procedural characteristics stratified by leukemia diagnosis

Patient Characteristics	No Leukemia Diagnosis (n=6,545,656)	Leukemia diagnosis (n=15,789)	p-value
Median age, years [IQR]	65 [56,74]	73 [65,80]	<0.001
Males	66.3%	72.8%	<0.001
Ethnicity			<0.001
White	63.2%	72.2%	
Black	6.4%	3.8%	
Hispanic	5.4%	3.2%	
Asian/Pacific Islander	1.8%	0.9%	
Native American	0.5%	0.4%	
Other	2.9%	1.9%	
Missing Ethnicity	20.0%	17.7%	
Elective admission	27.4%	23.4%	<0.001
Admission type – Weekday	83.9	83.1	0.009
Median ZIP income			<0.001
1st quartile	26.4%	22.7%	
2nd quartile	26.8%	27.4%	
3rd quartile	24.8%	24.1%	
4th quartile	22.0%	25.8%	
Expected Primary Payer			<0.001
Medicare	51.2%	74.7%	
Medicaid	5.7%	2.5%	
Private	34.6%	19.5%	
Uninsured	4.9%	1.0%	
No charge	0.5%	0.1%	
Other	2.8%	2.1%	
Unknown	0.2%	0.1%	

Procedure Details			
Single vessel PCI	72.7%	70.8%	<0.001
Multi-vessel PCI	17.9%	20.7%	<0.001
Unknown vessel number	9.4%	8.5%	<0.001
Bifurcation stenting	1.7%	1.9%	0.01
Use of assist devise or IABP	3.3%	3.4%	0.415
Bare Metal Stent	22.0%	30.3%	<0.001
Drug Eluting Stent	73.2%	64.1%	<0.001
Unknown Stent Type	6.9%	8.1%	<0.001
Both stent types used	2.2%	2.5%	<0.001
Fractional flow reserve	0.7%	1.2%	<0.001
Intravascular ultrasound	4.9%	5.4%	0.01
Record Characteristics			
STEMI diagnosis during hospitalization	22.8%	19.5%	<0.001
NSTEMI diagnosis during hospitalization	22.8%	28.2%	<0.001
Diagnosis of Shock	2.8%	3.8%	<0.001
Median length of stay, days [IQR]	2 [1,4]	3 [1,5]	<0.001
Median total charge, $ [IQR]	$17440 [$12962, $24263]	$19282 [$14124, $27156]	<0.001
Comorbidities			
Hypercholesterolemia	13.5%	11.8%	<0.001
Smoking	35.4%	26.2%	<0.001
Aids	0.1%	0.03%	0.08
Alcohol abuse	2.0%	0.9%	<0.001
Anemias	8.7%	16.4%	<0.001
Rheumatoid arthritis/collagen vascular diseases	1.8%	2.3%	<0.001
Congestive heart failure	1.0%	2.2%	<0.001
Chronic Pulmonary disease	15.5%	19.6%	<0.001
Coagulopathy	2.2%	11.3%	<0.001

Depression	5.4%	5.5%	0.296
Diabetes,	33.3%	32.2%	<0.001
Drug abuse	1.3%	0.7%	<0.001
Hypertension	69.7%	65.9%	<0.001
Hyperthyroidism	7.8%	10.1%	<0.001
Liver disease	0.8%	0.8%	0.360
Fluid & electrolyte disorders	9.3%	13.8%	<0.001
Other Neurological disorders	2.9%	3.4%	<0.001
Obesity	12.2%	8.8%	<0.001
Paralysis	0.7%	10.3%	<0.001
Peripheral vascular disorder	10.3%	12.4%	<0.001
Psychoses	1.3%	1.4%	0.938
Pulmonary circulation disorders	0.2%	0.3%	<0.001
Renal Failure	9.6%	15.5%	<0.001
Peptic ulcer disease excluding bleeding	0.03%	0.09%	<0.001
Valvular disease	0.3%	0.8%	<0.001
Weight loss	0.8%	1.4%	<0.001
Metastatic cancer	0.3%	0.5%	<0.001
Lymphoma	0.3%	1.9%	<0.001
Previous MI	13.2%	14.5%	<0.001
Previous PCI	18.9%	19.9%	<0.001
Previous CABG	7.4%	7.8%	<0.001
Previous TIA/stroke3	3.8%	5.8%	<0.001

Table 2: Patient demographics and procedural characteristics stratified by type of leukemias

Patient Characteristics	No Leukemia (n=6,545,656)	AML (n=1,023)	CML (n=2,275)	ALL (n=210)	CLL (n=10,800)	p-value

Median age, years [IQR]	65 [56,74]	69[59,76]	68 [59,76]	64 [53,72]	74 [67,81]	<0.001
Males	66.3%	71.0%	71.2%	72.7%	73.5%	<0.001
Ethnicity						<0.001
White	63.2%	66.4%	72.3%	63.6%	73.9%	
Black	6.4%	3.3%	4.8%	6.8%	3.4%	
Hispanic	5.4%	3.7%	4.4%	6.8%	2.4%	
Asian/Pacific Islander	1.8%	2.3%	3.4%	0%	0.3%	
Native American	0.5%	0.5%	0.2%	0%	0.4%	
Other	2.9%	1.4%	1.1%	4.6%	1.9%	
Missing Ethnicity	20.0%	22.4%	13.5%	18.2%	17.7%	
Admission type - Elective	27.4%	18.9%	19.5%	25.0%	23.9%	<0.001
Admission Day - Weekday	84.0%	79.0%	83.4%	84.1%	83.6%	0.001
Median ZIP income						<0.001
1st quartile	26.4%	21.0%	25.2%	13.6%	22.2%	
2nd quartile	26.8%	29.5%	27.9%	25.0%	26.8%	
3rd quartile	24.8%	22.9%	21.6%	20.5%	25.0%	
4th quartile	22.0%	26.6%	25.2%	40.9%	26.0%	
Expected Primary Payer						<0.001
Medicare	51.2%	65.4%	68.1%	52.3%	78.3%	
Medicaid	5.7%	5.6%	3.2%	2.7%	1.9%	
Private	34.6%	25.7%	25.4%	10.9%	17.0%	
Uninsured	4.9%	0.5%	1.3%	0%	0.8%	
No charge	0.5%	0.5%	0.2%	0%	0%	
Other	2.8%	1.4%	1.9%	4.6%	2.0%	
Unknown	0.2%	0.9%	0%	0%	0.04%	
Procedure Details						
Single vessel PCI	72.7%	72.9%	70.8%	77.3%	70.4%	<0.001
Multi-vessel PCI	17.9%	17.3%	21.9%	9.1%	21.2%	<0.001
Unknown vessel number	9.4%	9.8%	7.3%	13.6%	8.4%	<0.001
Bifurcation stenting	1.7%	2.3%	2.7%	0%	1.8%	<0.001
Use of assist devise or IABP	3.3%	3.3%	2.9%	4.6%	3.5%	0.584

Bare Metal Stent	22.0%	39.7%	31.1%	45.5%	28.9%	<0.001
Drug Eluting Stent	73.2%	49.1%	62.6%	50.0%	66.1%	<0.001
Unknown Stent Type	6.9%	12.6%	8.6%	4.5%	7.7%	<0.001
Both stent types used	2.2%	1.4%	2.3%	0%	2.7%	<0.001
Fractional flow reserve	0.7%	2.3%	1.3%	4.6%	1.0%	<0.001
Intravascular ultrasound	4.9%	6.1%	7.4%	6.8%	4.8%	<0.001
Record Characteristics						
STEMI diagnosis during hospitalization	22.8%	30.4%	17.7%	47.7%	18.3%	<0.001
NSTEMI diagnosis during hospitalization	22.8%	29.0%	33.2%	18.2%	27.7%	<0.001
Diagnosis of Shock	2.8%	8.4%	2.3%	9.1%	3.6%	<0.001
Median length of stay, days [IQR]	2 [1,4]	4 [2,8]	3 [2,6]	3 [2,14]	3 [1,5]	<0.001
Median total charge, $ [IQR]	$17440 [$12962, $24263]	$21289 [$15759, $33344]	$19193 [$14193, $28038]	$24821 [$14169, $45332]	$19339 [$14207, $26762]	<0.001
Comorbidities						
Hypercholesterolemia	13.5%	8.9%	9.0%	4.6%	12.4%	<0.001
Smoking	35.4%	27.1%	28.6%	18.2%	25.0%	<0.001
Aids	0.1%	0.5%	0%	0%	0%	<0.001
Alcohol abuse	2.0%	1.4%	0.2%	0%	1.0%	<0.001
Anemias	8.7%	15.0%	21.2%	13.6%	16.0%	<0.001
Rheumatoid arthritis/collagen vascular diseases	1.8%	2.8%	3.2%	2.3%	2.0%	<0.001
Congestive heart failure	1.0%	5.2%	2.1%	15.9%	1.6%	<0.001
Chronic Pulmonary disease	15.5%	17.3%	22.1%	18.2%	19.7%	<0.001
Coagulopathy	2.2%	20.1%	8.6%	6.8%	11.5%	<0.001
Depression	5.4%	6.5%	7.8%	4.6%	5.0%	<0.001
Diabetes	33.3%	29.5%	38.9%	34.1%	30.6%	<0.001
Drug abuse	1.3%	1.4%	1.1%	0%	0.5%	<0.001
Hypertension	69.7%	61.2%	68.5%	63.6%	65.4%	<0.001
Hyperthyroidism	7.8%	10.3%	11.3%	9.1%	9.7%	<0.001
Liver disease	0.8%	1.4%	1.1%	0%	0.6%	0.006
Fluid & electrolyte disorders	9.3%	25.6%	14.5%	27.3%	12.3%	<0.001
Other Neurological disorders	2.9%	3.3%	3.6%	2.3%	3.4%	0.001

Obesity	12.2%	11.2%	12.6%	13.6%	7.7%	<0.001
Paralysis	0.7%	0%	0.4%	0%	1.0%	<0.001
Peripheral vascular disorder	10.3%	11.7%	13.0%	6.8%	12.5%	<0.001
Psychoses	1.3%	3.7%	1.5%	0%	1.0%	<0.001
Pulmonary circulation disorders	0.2%	0.9%	0.6%	0%	0.2%	<0.001
Renal Failure	9.6%	15.0%	20.0%	4.6%	15.0%	<0.001
Peptic ulcer disease excluding bleeding	0.03%	0%	0.4%	0%	0.04%	<0.001
Valvular disease	0.3%	3.3%	0.2%	0%	0.6%	<0.001
Weight loss	0.8%	3.3%	1.3%	9.1%	1.0%	<0.001
Lymphoma	0.3%	0.5%	1.1%	4.6%	2.0%	<0.001
Metastatic cancer	0.3%	0.5%	0.2%	0%	0.6%	<0.001
Previous MI	13.2%	11.2%	15.1%	15.9%	14.3%	<0.001
Previous PCI	18.9%	18.7%	22.5%	25.0%	19.7%	<0.001
Previous CABG	7.4%	4.2%	6.5%	6.8%	8.2%	<0.001
Previous TIA/stroke	3.8%	3.35	6.3%	0%	5.6%	<0.001

Table 3: In-hospital mortality and complications stratified by leukemia diagnosis

	No Leukemia (n=6,545,656)	Leukemia (n=15789)	p-value
In-hospital mortality	1.6%	3.3%	<0.001
Any complication	9.0%	14.7%	<0.001
Bleeding complication	3.3%	8.7%	<0.001
Vascular complication	1.0%	1.5%	<0.001
Cardiac complication	3.0%	3.0%	0.842
Post-operative stroke	2.9%	3.0%	0.126

Table 4: Odds ratios* (OR) and 95% confidence intervals (CI) for patients with a leukemia diagnosis compared to those without.

	OR (95% CI)	p-value
In hospital mortality	1.41 (1.11,1.79)	<0.001
Any complication	1.21 (1.09,1.34)	<0.001
Bleeding complication	1.81 (1.56,2.09)	<0.001
Vascular complication	1.17 (0.87,1.56)	NS
Cardiac complication	0.76 (0.61,0.94)	<0.001
Post-operative stroke	0.77 (0.63,0.95)	<0.001

*Reference group is No Leukemia; adjusted for age, gender, median income, expected payer, elective admission, weekend admission, primary diagnosis of MI, STEMI/NSTEMI diagnosis, diagnosis of shock, use of an assist device or IABP, the type of stent used, multi-vessel PCI, bifurcation stenting, fractional flow reserve, intravascular ultrasound, year of hospitalization, Elixhauser comorbidities, smoking status, hypercholesterolemia, and previous MI, PCI, CABG or stroke; NS: not statistically significant

Table 5: In-hospital mortality and complications stratified by type of leukemia diagnosis

	No Leukemia (n=6,545,656)	AML (n=1,023)	CML (n=2,275)	ALL (n=210)	CLL (n=10,800)	p-value
In-hospital mortality	1.6%	12.2%	1.7%	4.6%	2.6%	<0.001
Any complication	9.0%	28.5%	15.8%	22.7%	13.5%	<0.001
Bleeding complication	3.3%	22.0%	11.6%	18.2%	7.1%	<0.001
Vascular complication	1.0%	2.3%	1.0%	0%	1.6%	<0.001
Cardiac complication	3.0%	3.3%	2.5%	2.3%	3.2%	0.590
Post-operative stroke	2.9%	4.7%	3.2%	2.3%	2.9%	0.01

AML: acute myeloid leukemia; CML: chronic myeloid leukemia; ALL: acute lymphoid leukemia; CML: chronic lymphoid leukemia

Table 6: Odds ratios* (OR) and 95% confidence intervals (CI) for adverse events according to leukemia subtype.

	AML OR (95% CI)	p-value	CML OR (95% CI)	p-value	ALL OR (95% CI)	p-value	CLL OR (95% CI)	p-value
In hospital mortality	5.38 (2.94,9.76)	<0.001	0.69 (0.25,1.89)	NS	1.31 (0.25,6.75)	NS	1.05 (0.76,1.43)	NS
Any complication	2.65 (1.84,3.82)	<0.001	1.29 (0.96,1.73)	NS	2.24 (1.08,4.66)	<0.001	1.10 (0.96,1.26)	NS
Bleeding complication	5.81 (3.67,9.21)	<0.001	2.32 (1.31,3.35)	<0.001	4.81 (2.11,10.96)	<0.001	1.45 (1.21,1.74)	<0.001
Vascular complication	1.50 (0.62,3.64)	NS	0.79 (0.33,1.90)	NS	**	**	1.23 (0.85,1.76)	NS
Cardiac complication	0.51 (0.22,1.19)	NS	0.65 (0.35,1.20)	NS	0.32 (0.03,3.34)	NS	0.83 (0.64,1.08)	NS
Post-operative stroke	1.42 (0.73,2.76)	NS	0.92 (0.54,1.58)	NS	1.11 (0.14,8.62)	NS	0.73 (0.56,0.93)	<0.001

*****Reference group is No Leukemia; adjusted for age, gender, median income, expected payer, elective admission, weekend admission, primary diagnosis of MI, STEMI/NSTEMI diagnosis, diagnosis of shock, use of an assist device or IABP, the type of stent used, multi-vessel PCI, bifurcation stenting, fractional flow reserve, intravascular ultrasound, year of hospitalization, Elixhauser comorbidities, smoking status, hypercholesterolemia, and previous MI, PCI, CABG or stroke; **NS:** not statistically significant; ****** Perfect predictor; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; ALL: acute lymphoid leukemia; CML: chronic lymphoid leukemia

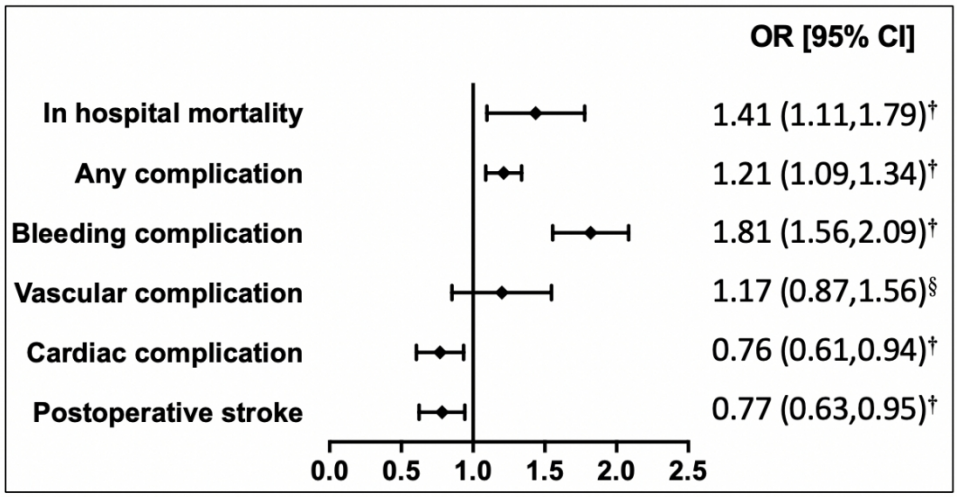
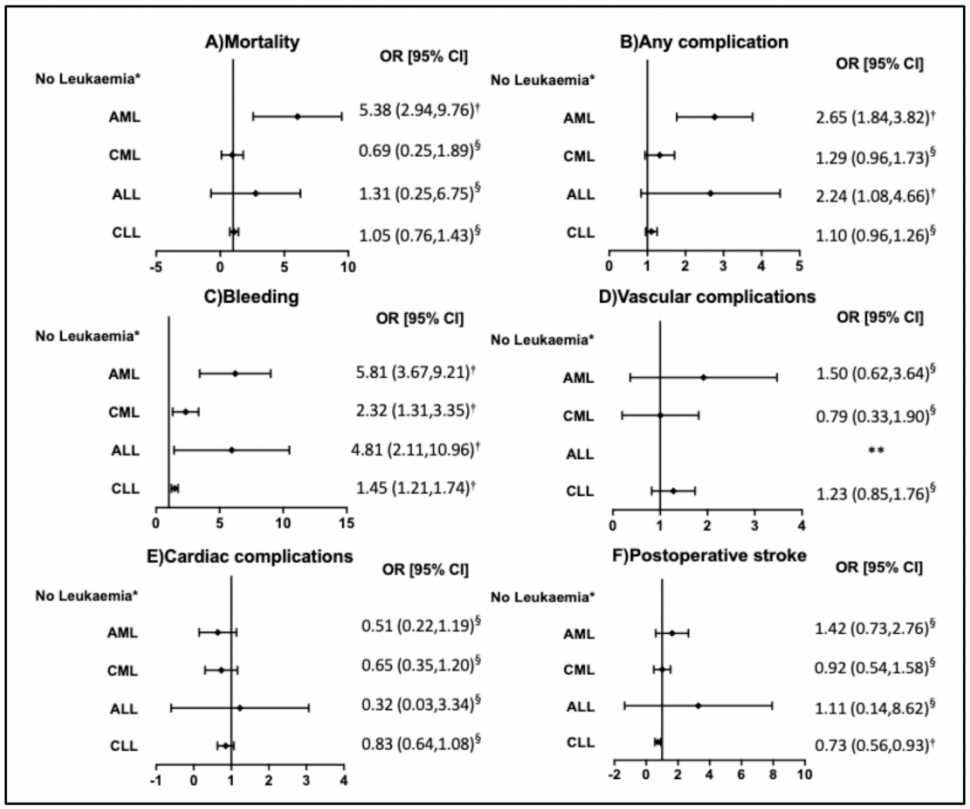
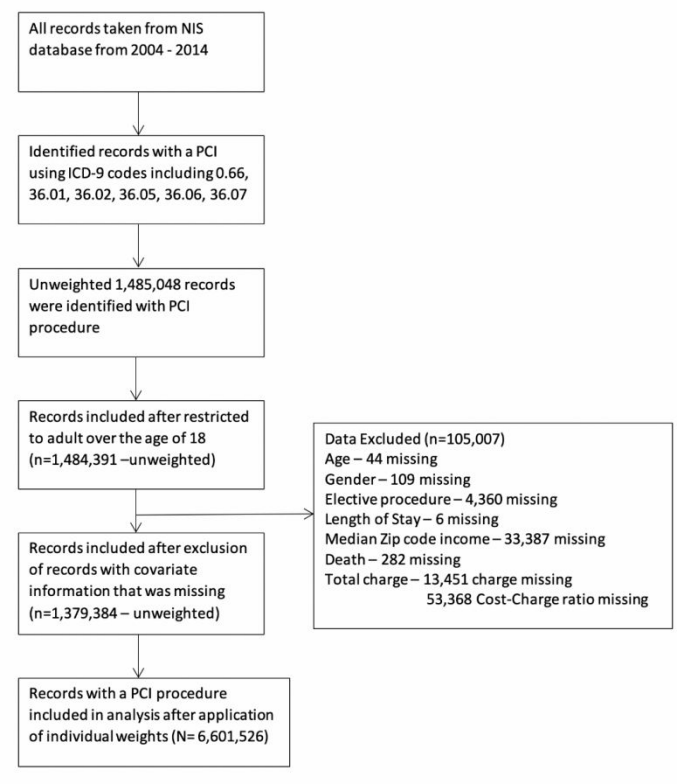


Figure 1. Adjusted odds ratio (OR) of adverse events in leukemia

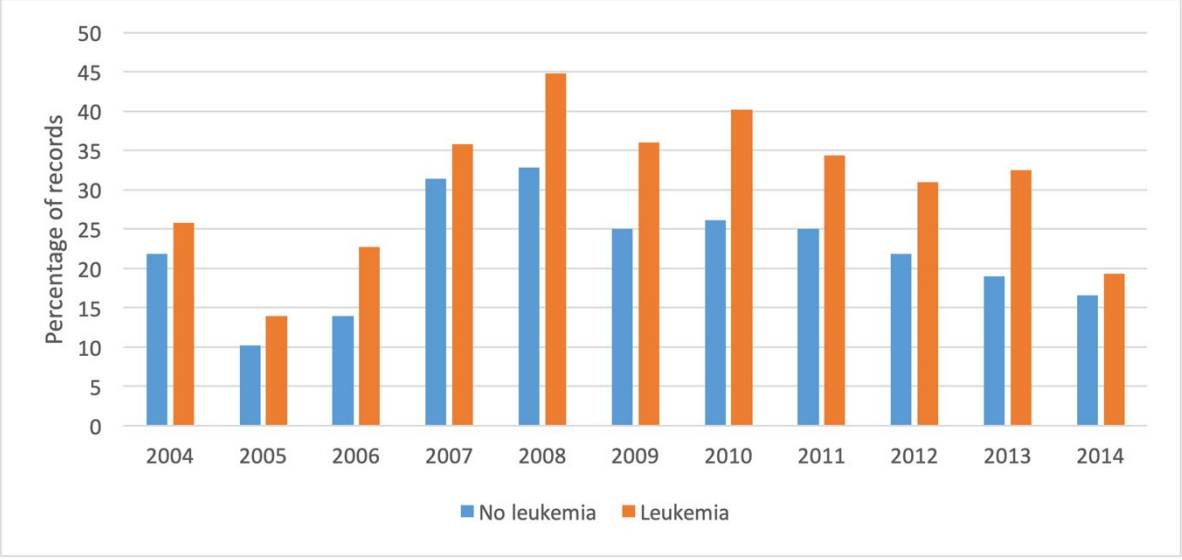


Adjusted odds ratio (OR) of adverse events according to leukemia subtype

Supplemental figure 1: Flow diagram of included records included in the analysis



Supplemental Figure 2: Percentage of records using bare metal stents over time stratified by leukemia diagnosis

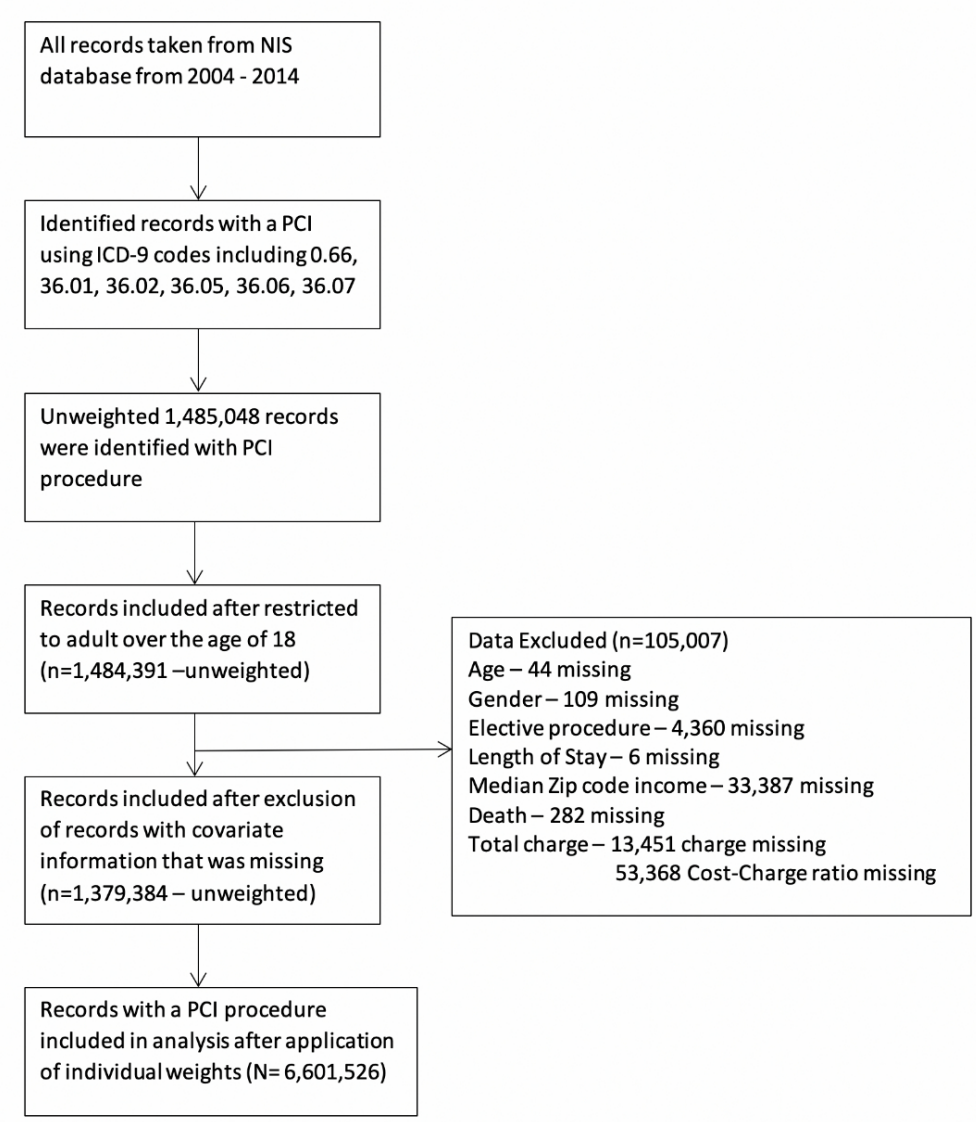


Supplementary table 1: ICD-9-CM codes for post procedural complications

Post-procedural Complication	**ICD-9-CM codes**
Bleeding complication	
Gastrointestinal	578.9
Unspecified haemorrhage	459.0
Retroperitoneal haemorrhage	568.81
Intracranial haemorrhage	432.9
Intracerebral haemorrhage	431.x
Blood transfusion	V58.2, 99.0x (procedure)
Vascular complications	
Post-op haemorrhage requiring transfusion	99.0 (procedure)
Vascular injury	900-904, 998.2, 447, 868.04, 999.7 (diagnosis) 39.31, 39.41, 39.49, 39.52, 39.53, 39.56 - 39.59 39.79 (procedure)
Cardiac complications	
Iatrogenic cardiac	997.1
Pericardial comp	423.0, 423.3 (diagnosis) 47.0 (procedure)
Requiring CABG	36.1x, 36.2, 36.31, 36.32, 36.9x
Post-op stroke/TIA	997.00-997.03, 430 – 437.9

Supplemental Table 2: Crude outcomes for individual bleeding complications stratified by leukemia type.

	No Leukemia Diagnosis (n=6,545,656)	AML (n=1,023)	CML (n=2,275)	ALL (n=210)	CLL (n=10,800)
Gastrointestinal	0.5%	0.5%	0.8%	2.3%	0.4%
Unspecified haemorrhage	0.07%	0.5%	0%	0%	0.05%
Retroperitoneal haemorrhage	0.04%	0%	0%	0%	0%
Intracranial haemorrhage	0%	0%	0%	0%	0%
Intracerebral haemorrhage	0.04%	0.4%	0%	0%	0%
Blood transfusion	2.8%	21.0%	11.2%	15.9%	6.9%



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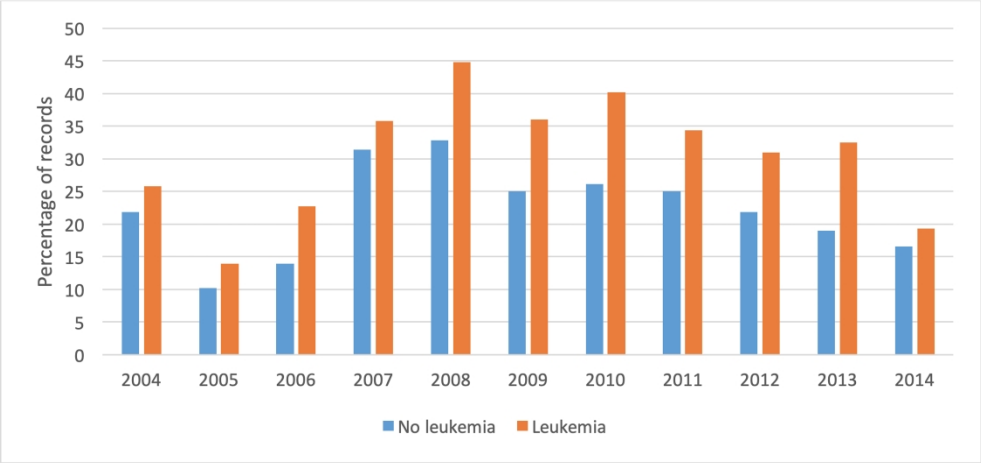

Supplementary figure 2

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