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Bleeding in hemato-oncology patients: beyond the platelet paradigm
Cornelissen, L.L.

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Chapter 4

Association between cardiovascular risk factors and intracranial hemorrhage in patients with acute leukemia

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Abstract

Background

Intracranial hemorrhage is seen more frequently in acute leukemia patients compared to the general population. Besides leukemia related risk factors, also risk factors that are present in the general population might contribute to hemorrhagic complications in leukemia patients. Of those, cardiovascular risk factors leading to chronic vascular damage could modulate the occurrence of intracranial hemorrhage in these patients, as during their disease and treatment acute endothelial damage occurs due to factors like thrombocytopenia and inflammation.

Objectives

Our aim was to explore if cardiovascular risk factors can predict intracranial hemorrhage in acute leukemia patients.

Methods

In a case control study nested in a cohort of acute leukemia patients, including 17 cases with intracranial hemorrhage and 55 matched control patients without intracranial hemorrhage, data on cardiovascular risk factors was collected for all patients. Analyses were performed via conditional logistic regression.

Results

Pre-existing hypertension and ischemic heart disease in the medical history were associated with intracranial hemorrhage, with an incidence rate ratio of 12.9 (95% confidence interval (CI) 1.5 to 109.2) and 12.1 (95% CI 1.3 to110.7), respectively.

Conclusion

Both pre-existing hypertension and ischemic heart disease seem to be strong predictors of an increased risk for intracranial hemorrhage in leukemia patients.

Introduction

Intracranial hemorrhage comprises intracerebral hemorrhage, subdural hemorrhage, epidural hemorrhage and subarachnoid hemorrhage.(1) In the general population, several risk factors have been described to be associated with the incidence of intracranial hemorrhage. These include male sex, higher age, African-American or Asian ethnicity, and trauma.(1-8) In addition, cardiovascular risk factors affecting the vascular wall, including hypertension, diabetes mellitus, smoking, and hypercholesterolemia have an effect on the risk of intracranial hemorrhage.(2, 4, 9, 10) More specifically, these cardiovascular risk factors are associated with intracerebral hemorrhage, while the other types of intracranial hemorrhage are more strongly associated with traumata or vascular malformations.(1)

Patients with acute leukemia have an increased risk for hemorrhage, including intracranial hemorrhage. Incidences of intracranial hemorrhage, during admission or follow-up in the outpatient clinic, are reported between 2.8% and 6.1%.(11-14) This incidence is much higher than what is observed in the general population, in which the incidence of intracerebral hemorrhage has been reported as 2.46/10,000 person-years.(15)

Specifically for acute promyelocytic leukemia (APL), a subtype of leukemia that is notorious for serious bleeding, it has been described that especially in the microvasculature of the brain, high annexin-2 and t-PA levels of the APL-cells contribute to intracranial hemorrhage.(16, 17) However, the biological mechanism underlying the high intracranial hemorrhage occurrence in the complete population of acute leukemia patients is not completely understood. Yet, in addition to disease and treatment associated thrombocytopenia, endothelial damage is known to be associated with an increased bleeding risk. The latter is likely to be a common phenomenon in this population, due to thrombocytopenia, inflammation, leukocytosis, graft versus host disease, and other disease and treatment related risk factors.(18-20) Therefore, all these factors could contribute to the observed increased risk of bleeding.(14, 21-26)

On top of these leukemia and treatment associated risk factors, other factors may also contribute to the occurrence of intracranial hemorrhage. Risk factors associated with chronic vascular damage in the general population can of course also be present in leukemia patients. Given the acute damage to their vessel walls, from which acute leukemia patients invariably suffer, the additional presence of pre-existing chronic damage to the vessel wall could act synergistically and be a relevant predictor of intracranial hemorrhage.

Therefore, we aimed to explore and estimate the predictive value of a history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic heart disease, overweight, obesity and smoking with the occurrence of intracranial hemorrhage among patients with acute leukemia.
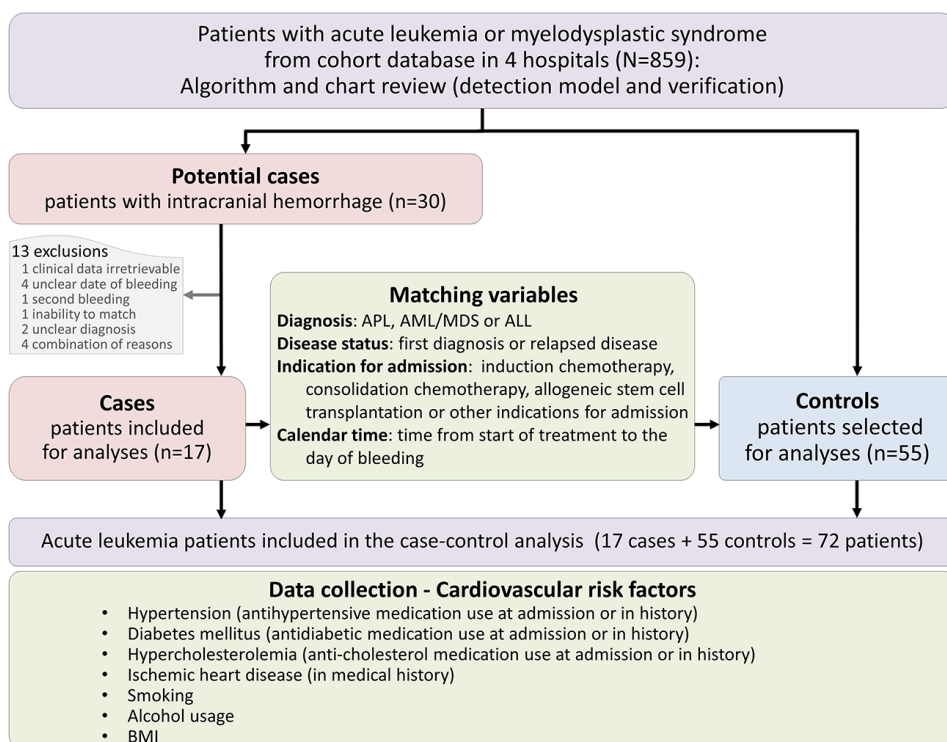
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Methods

Case identification and control matching

To assess the association of cardiovascular risk factors and intracranial hemorrhage, we performed a matched case control analysis, in an existing nested case control population of acute leukemia patients. As previously described, we used an automated algorithm to identify potential cases of intracranial hemorrhage, from a database with routinely collected clinical data, extracted from the electronic patient records of a cohort of patients with acute leukemia or myelodysplastic syndrome (MDS).(26, 27) Seventeen identified cases could be included for case control analysis and were matched to one to four control patients (Figure 1). Matching was performed on several likely major risk factors for bleeding, which in an unmatched population could mask true associations of other predictors: diagnosis (acute promyelocytic leukemia (APL); other acute myeloid leukemia (AML) or MDS; acute lymphoid leukemia (ALL)); indication for admission (induction chemotherapy; consolidation chemotherapy; allogeneic stem cell transplantation (SCT); other indications for admission); disease status (first diagnosis; relapsed disease) and time from start of treatment to the day of bleeding. Matching was performed according to incidence density sampling (i.e. matched on time, expressed as days since admission or start of chemotherapy), so the odds ratio would directly estimate the incidence rate ratio.(28)

The medical charts of patients selected as potential controls were checked for the absence of intracranial hemorrhage until the date matched to the bleeding date of the case patient (i.e. the index date(26)). Case patients could be selected as control patient for other case patients, if the date of intracranial hemorrhage was later than the matched date of bleeding for that case. Per case, we selected up to four control patients, based on availability. In total, 55 controls were selected. The total case control population therefore contained 72 patients (Figure 1). For all these patients, more extensive data than was already available from the database of electronic patient records was obtained via chart review and added to the existing dataset.

Variable definition

Information on hypertension, diabetes mellitus, dyslipidemia and ischemic heart disease was collected from the electronic patient record. Pre-existing hypertension was defined as any hypertension severe or persisting enough to lead to current use of antihypertensive medication, or registered medication use in medical history. Similarly, for diabetes mellitus and hypercholesterolemia evidence for any kind of glucose and cholesterol lowering medication current or in history was used. Mild diabetes or hypercholesterolemia, for example leading to lifestyle advices without the need for medication, were not included. Ischemic heart disease was defined as any prior diagnosis of ischemic heart disease.

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│         Patients with acute leukemia or myelodysplastic syndrome        │
│            from cohort database in 4 hospitals (N=859):                 │
│         Algorithm and chart review (detection model and verification)   │
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Potential cases
patients with intracranial hemorrhage (n=30)

13 exclusions
1 clinical data irretrievable
4 unclear date of bleeding
1 second bleeding
1 inability to match
2 unclear diagnosis
4 combination of reasons

Matching variables
Diagnosis: APL, AML/MDS or ALL
Disease status: first diagnosis or relapsed disease
Indication for admission: induction chemotherapy, consolidation chemotherapy, allogeneic stem cell transplantation or other indications for admission
Calendar time: time from start of treatment to the day of bleeding

Cases
patients included for analyses (n=17)

Controls
patients selected for analyses (n=55)

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Acute leukemia patients included in the case-control analysis (17 cases + 55 controls = 72 patients)

Data collection - Cardiovascular risk factors
- Hypertension (antihypertensive medication use at admission or in history)
- Diabetes mellitus (antidiabetic medication use at admission or in history)
- Hypercholesterolemia (anti-cholesterol medication use at admission or in history)
- Ischemic heart disease (in medical history)
- Smoking
- Alcohol usage
- BMI

Figure 1. Flowchart
Excluded cases did not differ substantially from included cases (see supplementary material table S1), although, as reason for exclusion, part had unclear diagnoses and more of the excluded patients were admitted for other reasons then disease modifying treatment. Inclusion period differed per hospital: hospital A June 2011 until March 2017, hospital B January 2010 until December 2015, hospital C January 2010 until December 2015, hospital D Jan 2013 until December 2015.

To collect information on alcohol use (yes/no) and smoking (current smoker, past smoker, never smoked or unknown) the doctor's notes in the charts were reviewed. Finally, the body mass index (BMI) on admission was also obtained from the electronic patient records, and categorized as normal, overweight (BMI 25-30) and obesity (BMI>30).(29) Missing data during the chart review was recorded in the category 'unknown' for the variables smoking, alcohol use and BMI.

In addition to the matching criteria, other variables collected to describe the study population were sex, age in years, all-cause mortality during admission, platelet count and use of anticoagulant medication or platelet aggregation inhibitors. Since the two latter can differ in time, we defined an index date for both cases and controls.(26) The index date was the date of bleeding for case patients and a time matched date for control patients. For platelet count we both registered the platelet count on the day before the index date, as well as the lowest platelet count in a week preceding the

index date. We defined the use of therapeutically dosed anticoagulant medication or platelet aggregation inhibitors as at least one dosage of medication in the ten days preceding the index date.

Prophylactic platelet transfusion policies

All hospitals applied to the at that time available nationwide guideline for platelet prophylaxis,(30) and platelet transfusions were administered at platelet counts below $10x10^9$/L. Higher platelet count thresholds could be applied when it was deemed necessary, but were not protocolized. Altered thresholds were not always noted in the medical records.

Statistical analysis

Because matching procedures create spurious associations of variables that are directly or indirectly associated with the matching variables, we performed matched analyses to remove these false associations.(31) Univariate matched conditional logistic regression models were used for each potential predictor. To analyze associations of cardiovascular risk factors with intracerebral hemorrhage, as a subtype of intracranial hemorrhage, we performed prespecified subgroup analyses for only the cases with such a bleeding focus. Here, we included both patients who had a solitary intracerebral hemorrhage, as well as patients who, based on the radiology reports, had an intracerebral hemorrhage combined with another location of intracranial hemorrhage. Although we already matched on diagnosis, as a post-hoc analysis, we performed a subgroup analysis based on diagnosis to explore the influence of the underlying disease on the results.

Ethical considerations

The medical ethical committee of the Leiden University Medical Center (LUMC) approved the study and waived the need for informed consent, for retrospective data collection, as did the other participating hospitals. The statistical analyses plan was approved, prior to analyses, by the Scientific Committee of the Department of Clinical Epidemiology of the LUMC, consisting of epidemiologists and statisticians.

Results

Description of the case control study population

The characteristics of the studied population are presented in Table 1. Since the case control ratio differed based on availability of eligible control patients, numbers and percentages are descriptive only and cannot be directly compared to those of case

Table 1. Characteristics of the study population

Matched variables*	Cases n=17	Controls n=55
Diagnosis (n, %)		
ALL	5 (29%)	19 (35%)
AML/MDS	11 (65%)	35 (64%)
APL	1 (6%)	1 (2%)
First diagnosis or recurrent disease (n, %)		
First diagnosis	12 (71%)	46 (84%)
Relapsed disease	5 (29%)	9 (16%)
Treatment phase (n, %)		
Remission induction	13 (76%)	47 (86%)
Consolidation therapy	1 (6%)	1 (2%)
Allogeneic SCT	1 (6%)	1 (2%)
Other	2 (12%)	6 (11%)
Non-matched variables		
Sex (n, %)		
female	8 (47%)	21 (38%)
male	9 (53%)	34 (62%)
Age [†] (median, IQR)	65 (52 to 70)	57 (42 to 68)
Platelet count (x10^9/L, median, IQR)		
Day before index date [‡]	21 (14 to 42)	30 (16 to 71)
Lowest value in a week [§]	11 (7 to 17)	15 (9 to 55)
Anti-coagulation and/or Platelet aggregation inhibitors [¶] (n, %)	5 (29%)	5 (9%)
Death[#] (n, %)	8 (47%)	5 (9%)

Values are numbers (percentage of total) unless otherwise specified.
* Since controls are matched to cases, numbers for matched variables presented for controls are dependent on control selection and therefore cannot be compared to numbers presented for cases. So, the observed similarities or differences between cases and controls, for these variables, is artificially induced by the number of eligible controls that were present, and cannot be interpreted in any other way.
† Age in years, median (IQR)
‡ lowest platelet count on the day before the index date (i.e. the date of bleeding for cases and a matched date for control patients)
§ lowest platelet count per patient, in the seven days before the index date
¶ At least one dose of platelet aggregation inhibitors or one therapeutic dose of anti-coagulant medication in an implicated period of 10 days before the index date. No patients were on double platelet aggregation inhibitors and/or anti-coagulation.
# all-cause mortality
Abbreviations: ALL: acute lymphoid leukemia, AML: Acute myeloid leukemia, MDS: myelodysplastic syndrome, APL: acute promyelocytic leukemia, SCT: stem cell transplantation, PAI: platelet aggregation inhibitors

patients. One AML case was matched to a control patient that was diagnosed with MDS, but treated as an AML.

For most baseline characteristics that were not matched, there were no relevant differences between case and control patients. All-cause mortality was substantially

higher in case patients; 47% deceased during admission, while this was 9% for the control patients. Also, cases more often use anti-coagulant medication or platelet aggregation inhibitors (29% in cases versus 9% in control patients).

Cardiovascular risk factors

The incidence rate ratio's (RR) and 95% confidence intervals (CI) for all cardiovascular risk factors are presented in Table 2. For hypertension, the rate ratio for intracranial hemorrhage was 12.9 (95% CI 1.5 to 109.2), indicating that patients on antihypertensive medication have a 12.9 times higher rate of intracranial hemorrhage compared to the patients who did not use or were never registered to use antihypertensive medication in their history. Additionally, ischemic heart disease was found to be associated with intracranial hemorrhage (rate ratio of 12.1; 95% CI 1.3 to 110.7).

   The risk factors diabetes mellitus type 2 (no patients suffered from type 1), hypercholesterolemia, smoking, and alcohol use also showed a positive association with intracranial hemorrhage. However, the wide confidence intervals precluded any firm conclusions about these factors. Finally, overweight and obesity, with a rate ratio approaching unity, were not associated with intracranial hemorrhage.

Subgroup analyses

In the general population cardiovascular risk factors are particularly associated with the intracerebral subgroup of intracranial hemorrhages. To assess if this was also the case in our patients, we performed predefined subgroup analyses selecting patients with intracerebral hemorrhage. Ten case patients and their 27 matched controls could be included in these analyses. Of these, one case patient had a combined intracerebral and subdural hemorrhage, three case patients had a combined intracerebral and subarachnoid hemorrhage and six case patients only had an intracerebral hemorrhage focus. The results for these subgroup analyses are presented in Table 2. While variability of estimates increases, due to the decreased sample size, overall direction of associations remains, suggesting little to no difference for this subgroup, compared to the whole study population. The risk factors hypercholesterolemia and ischemic heart disease could not be estimated in the subgroup analyses due to non-positivity (i.e., some (sub)categories did not contain patients due to the reduced sample size).

   In table S2, we present the RR for hypertension and ischemic heart disease per subgroup of diagnosis. Due to small numbers per subgroup not all RR's could be calculated, but the direction of the effect is similar in AML/MDS patients, and exclusion of patients with APL did not influence the results.

Table 2. RR's for cardiovascular risk factors on intracranial hemorrhage

Cardiovascular risk factors	Main analysis cases with intracranial hemorrhage (any type) and matched controls (complete case control population) N=72			Subgroup analysis only cases with intracerebral hemorrhage and matched controls N= 37		
	Cases	Controls	RR (95% CI)	Cases	Controls	RR (95% CI)
Hypertension						
No	9 (53%)	45 (82%)	reference	6 (60%)	23 (85%)	reference
Yes	8 (47%)	10 (18%)	12.9 (1.5 to 109.2)	4 (40%)	4 (15%)	6.7 (0.7 to 64.1)
Diabetes						
No	15 (88%)	52 (95%)	reference	9 (90%)	25 (93%)	ref
Yes	2 (12%)	3 (5%)	2.7 (0.4 to 20.5)	1 (10%)	2 (7%)	1.7 (0.1 to 30.8)
Hypercholesterolemia						
No	16 (94%)	52 (95%)	reference	10(100%)	27(100%)	reference
Yes	1 (6%)	3 (5%)	1.4 (0.1 to 16.4)	0(0%)	0(0%) -	†
Ischemic heart disease						
No	13 (76%)	53 (96%)	reference	8 (80%)	27 (100%)	reference
Yes	4 (24%)	2 (4%)	12.1 (1.3 to 110.7)	2 (20%)	0 (0%) -	†
Smoking						
Never	4 (24%)	26 (47%)	reference	3 (30%)	14 (52%)	reference
Yes, currently or past	8 (47%)	16 (29%)	3.5 (0.8 to 14.5)	6 (60%)	6 (22%)	4.7 (0.7 to 32.2)
Unknown	5 (29%)	13 (24%)	2.8 (0.6 to 13.0)	1 (10%)	7 (26%)	0.9 (0.1 to 10.6)
Alcohol use						
No	3 (18%)	16 (29%)	reference	2 (20%)	10 (37%)	reference
Yes	9 (53%)	22 (40%)	2.0 (0.5 to 8.6)	6 (60%)	6 (22%)	4.0 (0.6 to 25.5)
Unknown	5 (29%)	17 (31%)	1.3 (0.3 to 6.0)	2 (20%)	11 (41%)	0.4 (0.0 to 5.2)
BMI						
<25	8 (47%)	24 (44%)	reference	6 (60%)	15 (56%)	reference
25-30	4 (24%)	19 (35%)	0.9 (0.2 to 4.3)	1 (10%)	6 (22%)	0.6 (0.1 to 7.7)
>30	2 (12%)	9 (17%)	1.0 (0.2 to 6.4)	1 (10%)	3 (11%)	2.3 (0.1 to 51.5)
Unknown	3 (18%)	3 (5%)	7.2 (0.6 to 89.2)	2 (20%)	3 (11%)	4.6 (0.2 to 94.2)

Values represent the number of patients (%).
† no RR provided due to non-positivity
Hypertension: defined by need for antihypertensive medication at admission or in the medical history; Diabetes mellitus: defined as need for anti-diabetic medication in the medical history (so mild diabetes without need for medication is not included); High cholesterol levels: defined as need for cholesterol lowering agents at admission or in the medical history; Ischemic heart disease: defined as presence in medical history; Smoking: categorial variable divided in: yes (smoking currently or in past), no (registered as never smoked), unknown; Alcohol: categorial variable divided in: uses alcohol at all, never uses alcohol, unknown; BMI: body mass index score that was available at the day closest to the index date. <25 is a normal weight, 25-30 is overweight and >30 is obesity.

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Discussion

In this nested, matched case control study, we observed that in patients with acute leukemia, pre-existent hypertension and a history of ischemic heart disease were both strongly associated with an increased risk of intracranial hemorrhage.

Although the study has a small sample size, and therefore the precision of the magnitude of the association is suboptimal, a strength of our study is the matched case control study design with up to four controls per case patients. This design ensured optimal exploration of the included population, with a maximum of the potential power for intracranial hemorrhage as important bleeding outcome.(32) A limitation of our study is that, due to the chosen study objective and the small sample size, the observed associations cannot be explained as causality. The aim of our current study was to explore predictive values. However, it would also be of interest to study these associations etiologically, thus with correction for confounders. Yet, this would require a much larger dataset. Another limitation is that, given the matched case control design, predictive values, sensitivity and specificity of the cardiovascular risk factors could not be generated. For this purpose, a cohort study design would be necessary.

With a prevalence of approximately 31% in adults, (33) hypertension is highly prevalent in the general population, but even more so in patients with intracranial hemorrhage. It has been reported that 64% to 76% of patients with intracerebral hemorrhage and 38-42% of patients with other subtypes of intracranial hemorrhages were already diagnosed with hypertension prior to the intracranial hemorrhage.(34-36) This association could be explained by accumulating degenerative changes to the small vessels, resulting in an increased risk of ruptures of the small arterioles.(37, 38)

In our acute leukemia population, the risk of pre-existing hypertension, with a rate ratio of 12.90, shows to be substantially higher as compared to the general population. A meta-analysis of case control studies reported an overall odds ratio of 3.77 for the association between hypertension and the incidence of intracerebral hemorrhage in the general population.(2) However, a direct comparison of the meta-analyses data with our own results is not warranted for two reasons. First, the aforementioned meta-analysis included studies that analyzed only intracerebral hemorrhage while acute as well as pre-existing hypertension with and without need for medication were pooled. (2) The latter is important because hypertension might, next to indirectly via induction of chronic vascular changes, also be a direct acute cause of bleeding as well. Instead, we intended to analyze pre-existing hypertension only, defined as the need for medication at some point in medical history, but included all types of intracranial hemorrhage. Although it is likely that the increased risk is due to the specific leukemia population that was studied, these differences in bleeding outcomes and definitions of hypertension exposures may explain part of the difference in the magnitude of the

observed association between the former meta-analysis and our results. We did not include blood pressures during admission, since they may be affected by many factors that are only present during admission, and therefore may not reflect the level of pre-existing blood pressures. Second, given the wide confidence interval, the possibility that our result is overestimated also needs to be considered. However, given the high maximum likelihood estimation, it is most likely that the association of hypertension with intracranial hemorrhage in leukemia patients, is indeed higher as compared to the general population.

We also observed a similarly likely high association between ischemic heart disease in the medical history and intracranial hemorrhage. Indeed, patients with ischemic heart disease are known to have vascular damage of the coronaries, and are more likely to also have vascular damage elsewhere, like peripheral artery disease or cerebral vascular disease.(39) However, since five out of six patients who suffered ischemic heart disease in our population also (previously) used antihypertensive medication, our results for ischemic heart disease might also reflect the association of hypertension with intracranial hemorrhage.

The clear association of intracranial hemorrhage with cardiovascular risk factors like hypertension and ischemic cardiac disease that we observed, even in our small sample size study, was as we hypothesized. Whereas hematologists mostly focus on direct and mostly temporary leukemia specific risk factors, like biomarkers of hemostasis and coagulation, and clinical risk factors, this study demonstrates that also chronic pre-existing risk factors likely contribute to the bleeding risk. Leukemia and/ or its treatment associated thrombocytopenia not only compromises platelet dependent high flow system hemostasis, but also vascular wall integrity. The latter can also be aggravated by the administered therapy, inflammation or concurrent infections and thus multiplicate the cardiovascular risk.(18, 19, 40-42) While the precise contribution of all these factors in the observed rate ratios of course needs further research, both long standing hypertension and ischemic cardiac disease could in our opinion be viewed as a proxy for general pre-existing arterial damage.(37-39) This pre-existing arterial damage, together with the acute risk factors for vascular damage and bleeding that is specific for (treated) leukemia, could logically add to the observed high risk in leukemia for intracranial hemorrhage. Hence, it can explain the association of intracranial hemorrhage with cardiovascular risk factors. Although our current study only demonstrates the predictive power of these two risk factors, it would also be of interest to investigate causal associations. This would, however, only be possible in a larger dataset, with sufficient power for multivariate adjusted analyses. Besides giving better clues for causality, larger datasets could in the future also lead to multivariate prediction models that include both the relevant chronic risk factors like hypertension, and transient leukemia associated risk factors or biomarkers of hemostasis and coagulation.

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For the other CVD-associated conditions (diabetes mellitus, hypercholesterolemia, smoking, alcohol use), except for overweight or obesity, we also observed positive associations. Although in line with our further findings and hypothesis, our small sample size led to wide confidence intervals and hamper solid conclusions about the effect size and direction of the associations.

In the current study, we were unable to investigate if the predictive effect is different for patients with long term use of antihypertensive medication, or patients who need high dosages of these drugs. For example, we were unable to divide hypertension in groups of patients who had (a substantial period) of adequate hypertension control with medication, or patients who were still hypertensive while using antihypertensive medication. Since time of exposure to hypertension (with inadequate control) can contribute to the amount of vascular damage that is expected, this would be of interest to study in future. For the other risk factors, it would be also of interest to be able to divide into risk factors that are well controlled versus inadequate controlled for.

In addition, we investigated intoxications. For alcohol, although a less classical risk factor, not only the total amount but also the pattern of drinking has been described as cardiovascular risk factor.(43, 44) Although details on alcohol use were only available for 31 patients, high alcohol intake did not seem to differ between the cases and controls, with respectively one case (11%) on average drinking > 14 units of alcohol each week, compared to three (14%) of the control patients. A dose and time dependent relation is also known for smoking and the risk of cardiovascular disease.(45) Again, for only eight of our patients an estimation of the pack-years was available. Although for three cases the median package years was 35 (IQR 20 to 35) and for 5 controls the median was 25 (IQR 10-34), these data are insufficient for a corroborating conclusion.

We observed that patients with an intracranial hemorrhage died more often during admission compared to patients without intracranial hemorrhage. Although it has been described that intracranial hemorrhage in leukemia patients leads to a high mortality rate,(12) based on our data we cannot distinguish which patients died directly due to intracranial hemorrhage, and which patients had other causes of death.

While we currently focused on intracranial hemorrhage, being one of the most feared and serious bleeding events, patients with acute leukemia are also at risk for bleedings in other organ systems. It might be hypothesized that cardiovascular risk factors, besides increasing the incidence of intracranial hemorrhage, are also associated with other clinically relevant bleeding events. Future research should investigate this hypothesis.

Conclusions

In conclusion, pre-existing hypertension and a history of ischemic heart disease seem strongly associated with intracranial hemorrhage in acute leukemia patients. Although we only studied their potential predictive power on intracranial hemorrhage, and we cannot claim any causal relations, the observed associations are in line with the known causality between cardiovascular risk factors and vascular damage.

If confirmed in larger data sets, with more precise estimates, these cardiovascular risk factors may eventually be used to identify leukemia patients with an increased risk for intracranial hemorrhage. The goal is to prevent this complication in these patients. Therefore, in patients with an increased risk, additional or altered bleeding preventive strategies should be studied, for example the effect of higher platelet transfusion thresholds or additional hemostatic medication. Also, the effect of stricter regulation of hypertension in leukemia patients should be investigated.

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Summary statements

1. What is the new aspect of your work?
   While most studies investigating intracranial hemorrhage in leukemia focus on leukemia specific characteristics, we investigate the predictive value of cardiovascular risk factors to see if to what extend these predictors in the general population also apply to the population with acute leukemia.
2. What is the central finding of your work?
   A history of hypertension and/or ischemic heart disease seem strong predictors of intracranial hemorrhage in acute leukemia patients; the magnitude of this effect is likely higher compared to the general population.
3. What is (or could be) the specific clinical relevance of your work?
   Especially pre-existing hypertension may help to identify leukemia patients with a high risk of intracranial hemorrhage.

References

1. Tenny S, Thorell W. Intracranial Hemorrhage. StatPearls. Treasure Island (FL)2020.
2. Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke. 2003;34(8):2060-5.
3. Sturgeon JD, Folsom AR, Longstreth WT, Jr., Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke. 2007;38(10):2718-25.
4. An SJ, Kim TJ, Yoon BW. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. J Stroke. 2017;19(1):3-10.
5. Chen H, Guo Y, Chen SW, Wang G, Cao HL, Chen J, et al. Progressive epidural hematoma in patients with head trauma: incidence, outcome, and risk factors. Emerg Med Int. 2012;2012:134905.
6. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry. 2007;78(12):1365-72.
7. Flaherty ML, Woo D, Haverbusch M, Sekar P, Khoury J, Sauerbeck L, et al. Racial variations in location and risk of intracerebral hemorrhage. Stroke. 2005;36(5):934-7.
8. Labovitz DL, Halim A, Boden-Albala B, Hauser WA, Sacco RL. The incidence of deep and lobar intracerebral hemorrhage in whites, blacks, and Hispanics. Neurology. 2005;65(4):518-22.
9. Kapoor R, Pati HP, Mahapatra M, Monga A. Presence of Essential Hypertension or Diabetes Mellitus Is a Predictor of Intracranial Bleeding in Elderly Patients: A Study of 108 Patients with Isolated Thrombocytopenia from a Single Reference Center. Turk J Haematol. 2015;32(2):158-62.
10. Kwaan HC. Nonhematologic and Hematologic Factors in Spontaneous Intracerebral Hemorrhage. Semin Thromb Hemost. 2021.
11. Chen CY, Tai CH, Cheng A, Wu HC, Tsay W, Liu JH, et al. Intracranial hemorrhage in adult patients with hematological malignancies. BMC Med. 2012;10:97.
12. Chen CY, Tai CH, Tsay W, Chen PY, Tien HF. Prediction of fatal intracranial hemorrhage in patients with acute myeloid leukemia. Ann Oncol. 2009;20(6):1100-4.
13. Dayyani F, Mougalian SS, Naqvi K, Shan J, Ravandi F, Cortes J, et al. Prediction model for mortality after intracranial hemorrhage in patients with leukemia. Am J Hematol. 2011;86(7):546-9.
14. Koschade SE, Stratmann JA, Miesbach W, Steffen B, Serve H, Finkelmeier F, et al. Intracranial hemorrhage in newly diagnosed non-promyelocytic acute myeloid leukemia patients admitted for intensive induction chemotherapy. Eur J Haematol. 2021.
15. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol. 2010;9(2):167-76.
16. Kwaan HC, Huyck T. Thromboembolic and bleeding complications in acute leukemia. Expert Rev Hematol. 2010;3(6):719-30.
17. Kwaan HC, Weiss I, Tallman MS. The Role of Abnormal Hemostasis and Fibrinolysis in Morbidity and Mortality of Acute Promyelocytic Leukemia. Semin Thromb Hemost. 2019;45(6):612-21.
18. Goerge T, Ho-Tin-Noe B, Carbo C, Benarafa C, Remold-O'Donnell E, Zhao BQ, et al. Inflammation induces hemorrhage in thrombocytopenia. Blood. 2008;111(10):4958-64.
19. de Stoppelaar SF, van 't Veer C, Claushuis TA, Albersen BJ, Roelofs JJ, van der Poll T. Thrombocytopenia impairs host defense in gram-negative pneumonia-derived sepsis in mice. Blood. 2014;124(25):3781-90.
20. Maze D, Al-Abri M, Farooq K, Atenafu E, Nixon S, Lieberman L. Risk factors for intracranial hemorrhage in adults with acute leukemia. Transfusion. 2021.
21. Larsen AM, Leinoe EB, Johansson PI, Birgens H, Ostrowski SR. High syndecan-1 levels in acute myeloid leukemia are associated with bleeding, thrombocytopathy, endothelial cell damage, and leukocytosis. Leuk Res. 2013;37(7):777-83.
22. Rogers LR. Cerebrovascular complications in patients with cancer. Semin Neurol. 2010;30(3):311-9.
23. Zhang XH, Wang QM, Chen H, Chen YH, Han W, Wang FR, et al. Clinical characteristics and risk factors of Intracranial hemorrhage in patients following allogeneic hematopoietic stem cell transplantation. Ann Hematol. 2016;95(10):1637-43.
24. Najima Y, Ohashi K, Miyazawa M, Nakano M, Kobayashi T, Yamashita T, et al. Intracranial hemorrhage following allogeneic hematopoietic stem cell transplantation. Am J Hematol. 2009;84(5):298-301.
25. Velander AJ, DeAngelis LM, Navi BB. Intracranial hemorrhage in patients with cancer. Curr Atheroscler Rep. 2012;14(4):373-81.
26. Cornelissen LL, Kreuger AL, Caram-Deelder C, Middelburg RA, Kerkhoffs JLH, von dem Borne PA, et al. Thrombocytopenia and the effect of platelet transfusions on the occurrence of intracranial hemorrhage in patients with acute leukemia – a nested case-control study. Ann Hematol. 2020.

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27. Kreuger AL, Middelburg RA, Beckers EAM, de Vooght KMK, Zwaginga JJ, Kerkhoffs JH, et al. The identification of cases of major hemorrhage during hospitalization in patients with acute leukemia using routinely recorded healthcare data. PLoS One. 2018;13(8):e0200655.
28. Miettinen O. Estimability and estimation in case-referent studies. Am J Epidemiol. 1976;103(2):226-35.
29. World Health Organization: Obesity and Overweight fact sheet [Available from: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight.
30. de Vries R, Haas F, working group for revision of the Dutch Blood Transfusion G. English translation of the dutch blood transfusion guideline 2011. Clin Chem. 2012;58(8):1266-7.
31. Middelburg RA, Wiersum-Osselton JC, van de Watering LM, van der Bom JG. Observational etiologic research. Part 4--Matching in case-control studies: almost always a bad idea. Transfusion. 2014;54(2):267-70.
32. Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies. Lancet. 2005;365(9468):1429-33.
33. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. Circulation. 2016;134(6):441-50.
34. Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB. The Stroke Data Bank: design, methods, and baseline characteristics. Stroke. 1988;19(5):547-54.
35. Valentine D, Lord AS, Torres J, Frontera J, Ishida K, Czeisler BM, et al. How Does Preexisting Hypertension Affect Patients with Intracerebral Hemorrhage? J Stroke Cerebrovasc Dis. 2019;28(3):782-8.
36. Hevesi M, Bershad EM, Jafari M, Mayer SA, Selim M, Suarez JI, et al. Untreated hypertension as predictor of in-hospital mortality in intracerebral hemorrhage: A multi-center study. J Crit Care. 2018;43:235-9.
37. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. N Engl J Med. 2001;344(19):1450-60.
38. Caceres JA, Goldstein JN. Intracranial hemorrhage. Emerg Med Clin North Am. 2012;30(3):771-94.
39. Gersh BJ, Rihal CS, Rooke TW, Ballard DJ. Evaluation and management of patients with both peripheral vascular and coronary artery disease. J Am Coll Cardiol. 1991;18(1):203-14.
40. Zwaginga JJ. Platelets in infection-associated bleeding. Transfusion medicine / Platelets. 2014;8(411-420).
41. Smyth SS, McEver RP, Weyrich AS, Morrell CN, Hoffman MR, Arepally GM, et al. Platelet functions beyond hemostasis. J Thromb Haemost. 2009;7(11):1759-66.
42. Ypma PF, van Geloven N, Kerkhoffs JLH, Te Boekhorst P, Zwaginga JJ, Beckers EAM, et al. The association between haemorrhage and markers of endothelial insufficiency and inflammation in patients with hypoproliferative thrombocytopenia: a cohort study. Br J Haematol. 2020;189(1):171-81.
43. O'Keefe JH, Bybee KA, Lavie CJ. Alcohol and cardiovascular health: the razor-sharp double-edged sword. J Am Coll Cardiol. 2007;50(11):1009-14.
44. Minzer S, Losno RA, Casas R. The Effect of Alcohol on Cardiovascular Risk Factors: Is There New Information? Nutrients. 2020;12(4).
45. Lubin JH, Couper D, Lutsey PL, Woodward M, Yatsuya H, Huxley RR. Risk of Cardiovascular Disease from Cumulative Cigarette Use and the Impact of Smoking Intensity. Epidemiology. 2016;27(3):395-404.

Supplementary material

Table S1. Characteristics of included versus excluded cases for main analysis

Matched variables	Included cases n=17	Excluded cases n=13
Diagnosis (n, %)		
ALL	5 (29%)	2 (15%)
AML/MDS	11 (65%)	6 (46%)
APL	1 (6%)	2 (15%)
Unclear / unmatchable diagnosis	0 (0%)	3 (23%)
First diagnosis or recurrent disease (n, %)		
First diagnosis	12 (71%)	7 (54%)
Relapsed disease	5 (29%)	2 (15%)
Unclear	0 (0%)	2 (15%)
Treatment phase (n, %)		
Remission induction	13 (76%)	7 (54%)
Consolidation therapy	1 (6%)	0 (0%)
Allogeneic SCT	1 (6%)	0 (0%)
Other indications or untreated	2 (12%)	6 (46%)

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Table S2. RR's for a history of hypertension and ischemic heart disease on intracranial hemorrhage specified per diagnosis

APL		Total	Cases	Controls	RR (95% CI)
Hypertension	No	2 (100%)	1 (100%)	1 (100%)	reference
	Yes	0	0	0	*
Ischemic heart disease	No	2 (100%)	1 (100%)	1 (100%)	reference
	Yes	0	0	0	*
AML/MDS		**Total**	**Cases**	**Controls**	**RR (95% CI)**
Hypertension	No	31 (67%)	5 (45%)	26 (74%)	reference
	Yes	15 (33%)	6 (55%)	9 (26%)	8.3 (0.9 to 73.9)
Ischemic heart disease	No	42 (91%)	9 (82%)	33 (94%)	reference
	Yes	4 (9%)	2 (18%)	2 (6%)	4.7 (0.41-54.4)
ALL		**Total**	**Cases**	**Controls**	**RR (95% CI)**
Hypertension	No	21 (88%)	3 (60%)	18 (95%)	reference
	Yes	3 (12%)	2 (40%)	1 (5%)	*
Ischemic heart disease	No	22 (92%)	3 (60%)	19 (100%)	reference
	Yes	2 (8%)	2 (40%)	0	*
ALL or AML/MDS		**Total**	**Cases**	**Controls**	**RR (95% CI)**
Hypertension	No	52 (74%)	8 (50%)	44 (81%)	reference
	Yes	18 (26%)	8 (50%)	10 (19%)	12.9 (1.5 to 109.2)
Ischemic heart disease	No	64 (91%)	12 (75%)	52 (96%)	reference
	Yes	6 (9%)	4 (25%)	2 (4%)	12.1 (1.3 to 110.7)
All diagnosis combined		**Total**	**Cases**	**Controls**	**RR (95% CI)**
Hypertension	No	54 (75%)	9 (53%)	45 (82%)	reference
	Yes	18 (25%)	8 (47%)	10 (18%)	12.9 (1.5 to 109.2)
Ischemic heart disease	No	66 (92%)	13 (76%)	53 (96%)	reference
	Yes	6 (8%)	4 (24%)	2 (4%)	12.1 (1.3 to 110.7)

* Due to non-positivity or small group numbers, no relative risk could be calculated

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