Obesity and Initial High White Blood Cell Count Are Predictors of Thrombo-hemorrhagic Early Death in Children and adolescents with t(15;17) positive Acute Promyelocytic Leukemia

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Disclosures

- No Conflicts of Interest to disclose.

Background – Pediatric APL

- 5-10% of pediatric AML
- 10 year EFS - 80% with ATRA & Chemo
- 3 year EFS - 91% with ATRA/ATO & Chemo
- Early death (ED) rates - 3.6 to 7.5% in pediatric trials
- WBC > 10,000 and *FLT3*-ITD associated with ED

Testi et al, Blood, 2005
Kutny et al: PBC, 2012 & JCO, 2017

ED in Adult APL

- Population-based registries: 17-29%
  Clinical trials: 5 -10%

- ED predictors:
  - High WBC/blast count
  - Coagulopathy
  - Age > 60 years
  - Abnormal creatinine/albumin

- However, predictors of ED in pediatric APL are not well defined

de la Serna et al, Blood 2008
Lehmann et al, Leukemia, 2009
Park et al, Blood, 2010

Objectives

- To determine the incidence of thrombo-hemorrhagic early death (TH-ED) in children & adolescents with APL

- To determine clinical, biological and treatment predictors of TH-ED

Methods: ED defined as death within 30 days from Dx

Inclusion Criteria

- Age 0-20 years
- *de novo* APL
- Confirmed t(15;17) or *PML-RARα* fusion
- Treatment era: Jan1, 1993 and Dec 31, 2013

Exclusion Criteria

- Secondary APL & Rare Variants
- ATRA received only after induction
- ED before diagnosis or any treatment

Collected data

- Demographics, ethnicity, BMI
- Initial Labs: CBC, Coags, albumin, creatinine, CNS status
- APL morphology, CD56 & CD2, PML breakpoint, FLT3 mutation
- Treatment factors:
  - Time from presentation to 1st ATRA
  - Blood products given in 1st 24 hours
  - Induction therapy & use of steroid prophylaxis
  - Clinical trial & treatment period
- Causes of death and timing

Definitions

- Increased BMI: ≥ 95% according to WHO

- Elevated WBC: > 10 x 10^9/L

- Elevated PB blast count: > 30 x 10^9/L

Results

- 683 children from AIEOP, PETHEMA, BFM, Canada, NOPHO, DCOG, North American C9710, St Jude & Australia
- Treatment: ATRA + Chemotherapy – 97% were on clinical trials
- ATRA dose: 25 mg/m^2 ; 82 pts had dose of 45 mg/m^2 (C9710)
- Most groups kept PLTs > 30-50 x 10^9/L and Fibrinogen > 1.5 mg/L
- DS prophylaxis was not uniform – steroids at first suspicion of DS

Results: 683 patients

- Median age 12.7 years (0.4 - 19) - M:F = 1:1
- Median WBC count: 3.8 x 10^9/L (0.2 – 339) overall

  ED group 37.4 x 10^9/L (0.8 - 339)

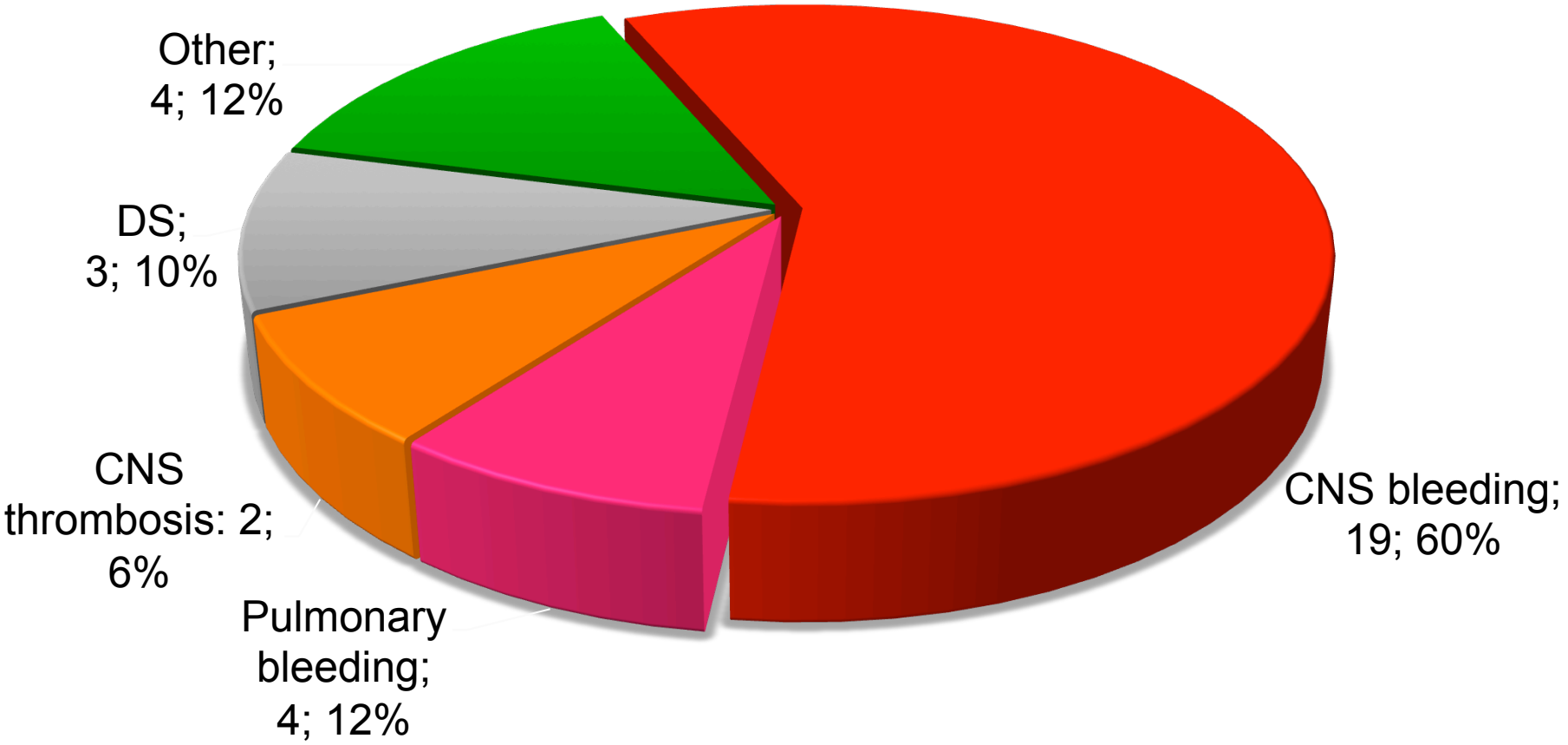
  Non-ED group 3.6 x 10^9/L (0.2 - 284)

- Elevated WBC: 217 (32%), 22 had ED = 71% of all ED

- Coags/albumin/creatinine/FLT3 – incomplete data

- **ED occurred in 32/683 (4.7%):** 25 related to bleeding or thrombosis , 7 due to other causes

Causes of Early Death- 32 events: 25 (78%)TH-ED



Timing of ED

- *Week 1*: 56% of ED (18/32) = 12 CNS bleeding, 2 pulm bleeding, 2 CNS thrombosis, 1 resp. failure & 1 multiorgan failure

- *Week 2*: 22% of ED (7/32): 5 CNS bleeding, 1 renal failure, 1 bacterial infection

- *Week 3*: 9% of ED (3/32): 1 CNS bleeding, 2 DS

- *Week 4:* 13% of ED (4/32): 1 CNS bleeding, 2 pulm. Bleeding, 1 DS

CD56 data: available in 33% (228/683)

- 17.6% (3/17) of CD56+ pts had ED: 2TH & 1 other
- 6.6% (14/211) of CD56- pts had ED
- Hard to make conclusions on CD56 role

Statistical Analysis- Primary Event: Fatal bleeding/thrombosis

- ED due to other causes – competing risk
- Gray's Test: statistical difference in cumulative incidence of pts with WBC > 10 *vs* < 10 x 10^9/L & normal BMI *vs* BMI ≥ 95%
- Cox proportional hazard regression: predictive factors of TH-ED
- Univariable models initially completed on clinically relevant features
- Variables at $P \leq 0.2$ and those clinically relevant → multivariable analysis

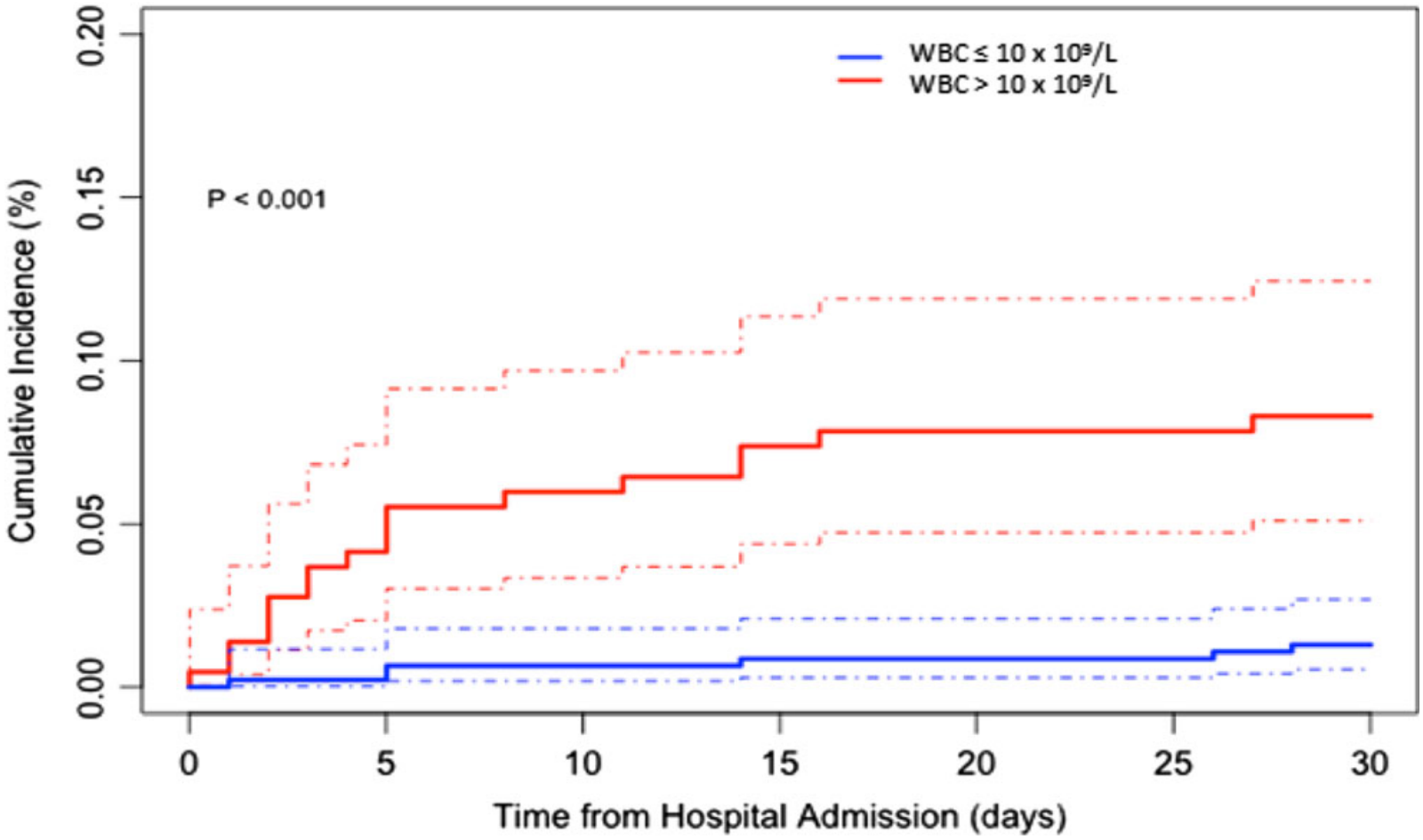
Table 2: Univariable Cox proportional hazard regression (HR) analysis of early death predictors for thrombohemorrhage in pediatric APL (n = 683)

Predictors	Hazard ratio	95% confidence Interval	*P* value	#of ED events (*N* total used in HR regression)
Age (>10 years)	1.34	0.56 – 3.21	0.51	25 (608)
Male	2.09	0.90– 4.83	0.09	25 (683)
Increased BMI	2.39	0.99 –5.77	0.05	21 (527)
Elevated WBC counts	6.63	2.64 –16.64	<0.001	24 (679)
Elevated PB blasts counts	10.52	4.64 –23.87	<0.01	23 (653)
Low platelet counts	0.72	0.17 –3.01	0.65	24 (677)
Hemoglobin	1.02	0.82 – 6.63	0.85	23 (673)
Micrograndular variant (M3*v*)	2.93	1.30 – 6.63	<0.001	25 (670)
Steroid prophylaxis	1.00	0.33 – 3.05	1.00	13 (433)
Black ethnicity	9.43	2.88 –30.82	<0.001	25 (683)
Cytarabine use in induction	2.20	0.98 –4.95	0.06	24 (676)
Treatment era: 1993 – 2002	1.17	0.53 –2.55	0.70	25 (683)

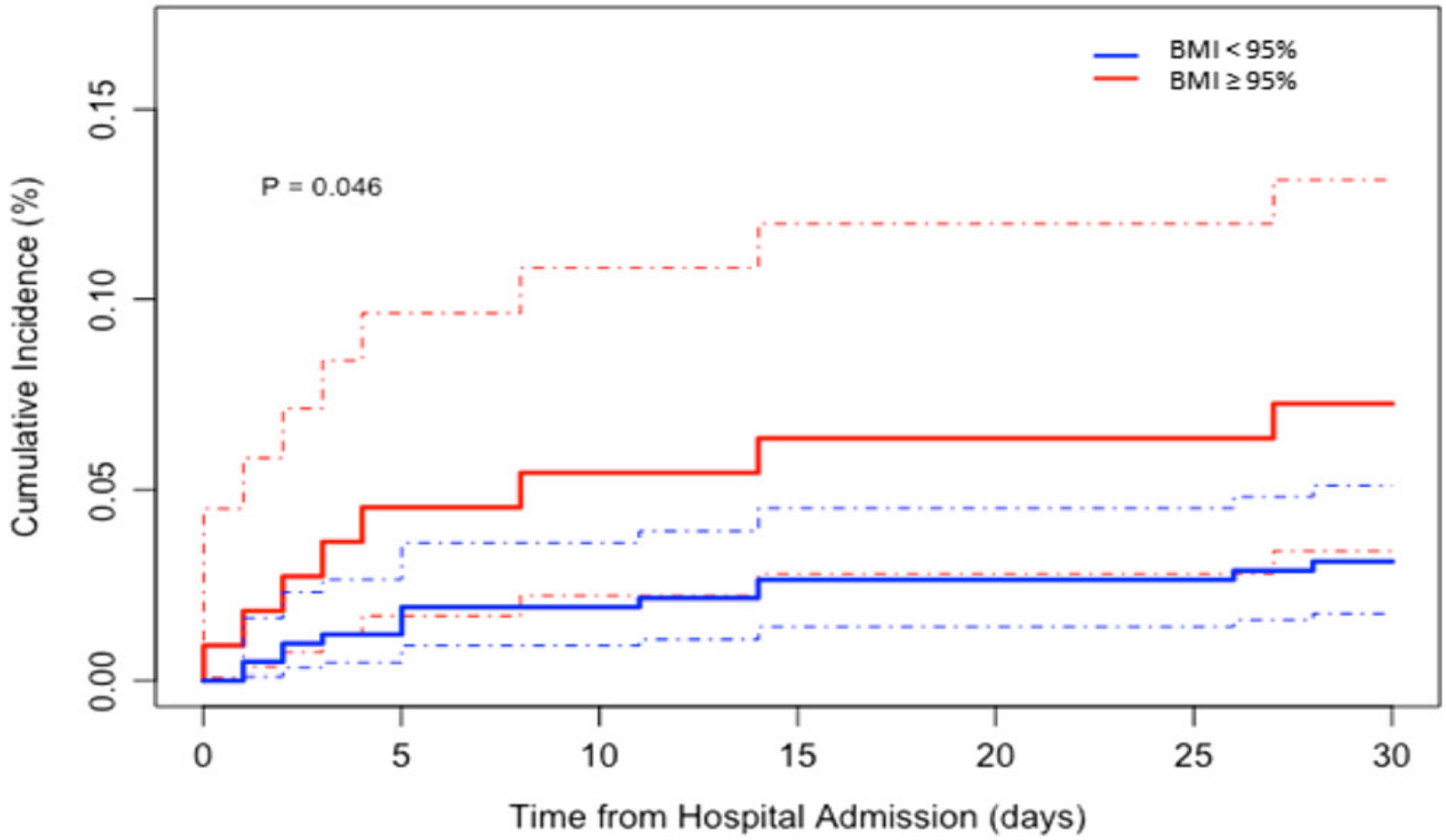
Table 3: Multivariate Cox regression analysis of significant thrombohemorrhagic early death predictors during induction

Predictors	Hazard Ratio	95% confidence interval	P value
Increased BMI	2.70	1.11 –6.59	0.03
Elevated WBC count	3.97	1.50—10.52	<0.01
Microgranular variant (M3*v*)	2.13	0.83—5.47	0.11

Incidence of Thrombohemorrhagic ED in Pediatric Patients According to Presenting White Blood Cell Count (WBC) – 95% Confidence Interval



Incidence of Thrombohemorrhagic ED for Pediatric Patients of Normal and Obese Weights – 95% Confidence Interval



Summary

- Bleeding and thrombosis are the leading causes (78%) of ED in childhood & adolescent APL
- CNS bleed: 23% survived beyond induction
- High WBC count & increased BMI: associated with TH-ED in pediatric APL

Discussion: Obesity And Cancer

- Obesity is more common in APL than other AML - adults and children

  Breccia et al, Blood, 2012
  Feusner et al, Blood, 2006

- Associated with DS and relapsed APL in adults treated with AIDA

- Associated with poor EFS/OS and TRM in Ped. ALL and AML (excluding APL)

  Orgel et al, Am J Clin Nutr. 2016
  Lange et al, JAMA, 2005

Obesity & Thrombosis/Bleeding

- Increased risk of ICH and ischemic stroke in obese adults without cancer

Pezzini et al, Stroke, 2013

- Increased thrombin/anti-thrombin complexes in obese children and young adults → ↑ thrombosis

Siklar et al, Clin Appl Thromb Hemost 2012

Hyperleukocytosis AND ED in APL

- Previous studies showed increased risk of relapse and ED in APL pts with WBC > 10 x10^9/L.

Testi et al, Blood, 2005

Sanz et al, Blood, 2000

- Higher risk of pulmonary & CNS bleeding: predicts fatal early bleeding in adults **Mantha et al, Blood, 2017**

Our Study:

- 63% of CNS bleeding - with WBC > 50 x 10^9/L

CNS bleeding: More Frequent in APL. Why?

- Unknown reasons

- Due to high concentration of ***Annexin II*** on APL blasts and on cerebral microvascular endothelial cells?

Limitations

- Incomplete data: retrospective, multinational
- Some clinically relevant predictors missed?
- Selection bias: mostly patients from clinical trials
- Heterogeneity of supportive care measures

Conclusions

- First study correlating obesity & TH-ED in APL
- High WBC/blast counts- poor prognostic factor in children
- CNS bleeding- strongly associated with ED in pts treated with ATRA/Chemo
- More effective treatment needed for APL-related DIC

Future Directions

- Obesity & high WBC: Can they predict TH-ED also in adults/children treated with ATO-based regimens?

- Prospective study of ED predictors in childhood APL – needed with pediatric ATO based trials

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