

Incidence, Risk Factors, and Complications Associated with Hypertension During Induction Chemotherapy Among Adolescent and Young Adult Patients with Acute Lymphoblastic Leukemia



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Background

Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood. Pediatric patients have been successfully treated by Berlin, Frankfurt, Muenster (BFM)-inspired regimens.¹ Since 2008, these regimens have been used the adolescent and young adult (AYA) population, who were previously treated with Hyper-CVAD.² Several studies from international groups demonstrated AYAs with ALL have increased overall survival on BFM-inspired regimens.^{3,4} BFM-inspired regimens utilize more intensive and longer courses of corticosteroids during induction and delayed intensification.^{5,6}

- In pediatric ALL patients, corticosteroids are known to cause several cardiometabolic disturbances such as hypertension (incidence 17.2%).⁷⁻¹⁰

Corticosteroid-related hypertension may lead to both short- and long-term cardiovascular sequelae. Limited data exists describing incidence, risk factors, and outcomes of corticosteroid-related hypertension in the AYA population. Current research has found the following:

- AYAs have an increased risk of developing hyperglycemia due to induction steroids and asparaginase, a known risk for cardiovascular disease¹¹
- Older patient age increases risk of osteonecrosis, which has been proposed to be due to corticosteroid-mediated vascular changes.¹²
- Pediatric ALL survivors were more likely to develop arterial hypertension within 10 years of treatment compared to healthy controls.¹³

Objectives

To describe the incidence, risk factors, and outcomes in AYA patients who develop hypertension during induction chemotherapy.

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Materials & Methods

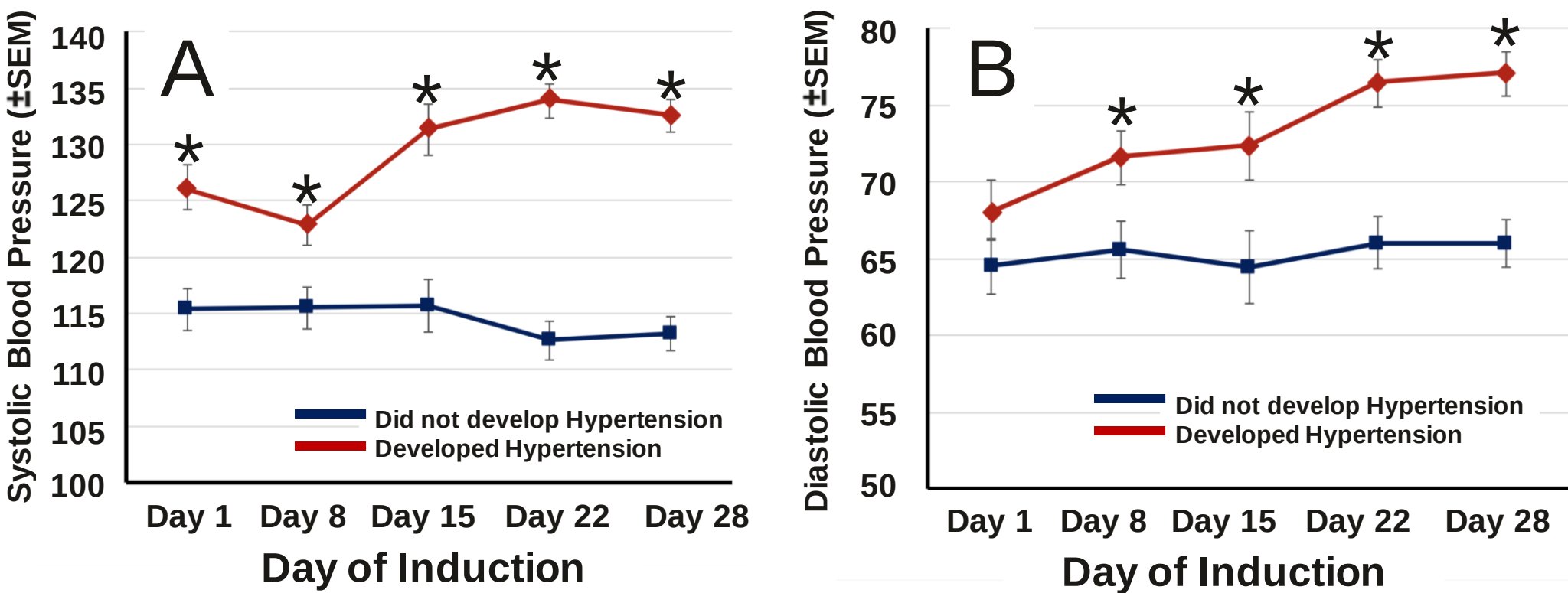
Patients and setting: 72 AYA patients diagnosed with ALL from 2009–2019 at a tertiary referral center. IRB protocol: **1804170562**

- **Mean age:** 17.2±2.8 years
- **Median follow-up from date of diagnosis:** 5.2 years

Hypertension graded per Common terminology criteria for adverse events, version 5 (CTCAE).

Patients divided into following groups:

- **Developed Hypertension:** Daily averaged systolic and/or diastolic pressure exceeded CTCAE grade of I–IV on days 8, 15, 22, or 28 for 2 points 2 weeks apart.
- **Did not develop Hypertension:** Daily averaged systolic and/or diastolic pressure remained grade 0 throughout induction



A: Systolic blood pressure at days 1, 8, 15, 22, and 28 of induction. * = P-value <0.05 (paired 2-tailed t-test)

B: Diastolic blood pressure at days 1, 8, 15, 22, and 28 of induction. * = P-value <0.05 (paired 2-tailed t-test)

- **Incidence of hypertension during induction:** 45 (63%) patients
- **Patients treated with anti-hypertensives at any point in ALL regimen:** 14 (31% of Developed Hypertension group)

Main Measures (data gathered from retrospective chart review):

- **Risk factors assessed:** age, sex, body surface area (BSA), body mass index (BMI), pre-induction blood pressure, renal function, tumor lysis laboratory values, and cumulative dose or type of steroid.
- **Outcomes assessed:** corticosteroid-related adverse effects (hyperglycemia, osteonecrosis), cardiac dysfunction (arrhythmia, systolic or diastolic dysfunction, or heart failure), PICU admissions, and 5-year relapse-free and overall survival rates.

Results

Risk Factors for developing hypertension:

Table 1:

	Comparison	Odds Ratio (95% Confidence Interval)
Biologic Sex	Male vs. Female	3.86 (1.39, 10.7)
Steroid Type	Dexamethasone vs. Prednisone	0.95 (0.28, 3.27)

Male sex is associated with increased likelihood of developing hypertension during induction chemotherapy. Odds ratios were calculated with 95% confidence intervals. P-value <0.05 is significant.

Table 2:

Pre-induction characteristics	Total	Hypertension during induction		
		No	Yes	P-Value
Age at Diagnosis (yr ± SD)	17.9 ± 2.8	18.5 ± 3.1	17.6 ± 2.6	0.21
Steroid Equivalent dose (mg/day ± SD)	3415.1 ± 685.0	3279.5 ± 611.7	3496.4 ± 719.7	0.20
Weight (kg ± SD)	78.8 ± 23.0	73.0 ± 19.3	82.2 ± 24.5	0.10
BMI (kg/m2 ± SD)	26.4 ± 6.8	26.3 ± 7.2	26.5 ± 6.7	0.89
BSA (m2 ± SD)	1.9 ± 0.3	1.8 ± 0.2	2.0 ± 0.3	0.03
Uric Acid (mg/dL ± SD)	7.6 ± 4.8	6.1 ± 2.2	8.4 ± 5.7	0.05
Creatinine (mg/dL ± SD)	1.0 ± 0.4	0.8 ± 0.2	1.0 ± 0.4	0.01
BUN (mg/dL ± SD)	14.9 ± 5.5	14.1 ± 5.5	15.3 ± 5.6	0.35
Systolic Blood Pressure (mmHg ± SD)	122.0 ± 13.4	115.3 ± 9.3	126.1 ± 13.9	0.00
Diastolic Blood Pressure (mmHg ± SD)	66.7 ± 8.7	64.5 ± 4.9	68.0 ± 10.1	0.10

BMI = Body mass index, BSA = Body surface area, BUN = Blood urea nitrogen. Patients who developed hypertension during induction had significantly higher baseline BSA, Uric Acid, and Creatinine, and pre-induction systolic blood pressure compared to patients who remained normotensive throughout induction. Baseline characteristics were compared using 2-tailed paired t-tests for continuous variables. P-value <0.05 is significant.

Outcomes of patients who developed Hypertension during induction:

Table 3:

Incidence of Following Outcomes:	Relative Risk (95% Confidence Interval)
Steroid-induced hyperglycemia	3.25 (1.26, 8.38)
Hypertensive emergency	1.24 (0.40, 4.52)
Osteonecrosis	1.78 (0.71, 4.42)
Post-induction Hypertension (recurrent or sustained)	1.93 (0.94, 3.96)
Cardiac dysfunction	0.91 (0.35, 2.39)
Relapse	0.93 (0.31, 2.85)
Pediatric ICU admission	0.26 (0.08, 0.81)
All-cause mortality	0.63 (0.32, 1.23)

PICU = pediatric intensive care unit
The development of hypertension during induction is associated with an increased risk of also having steroid-induced hyperglycemia. Conversely, hypertension during induction reduced the risk of being admitted to the PICU throughout entire course of ALL treatment regimen.

Summary

The majority (63%) of AYA patients developed hypertension during ALL chemotherapy induction.

Risk factors identified:

- Male sex (3.86-fold increase vs. Females)
- Increased baseline BSA, elevated pre-induction systolic blood pressure, decreased renal function, hyperuricemia

Outcomes: Hypertension during induction was

- Not associated with inferior survival rates or long-term cardiovascular sequelae.
- Associated with steroid-induced hyperglycemia and decreased admissions to the PICU at any point throughout total ALL treatment regimen

Discussion

Corticosteroids are the only induction medications with hypertension listed as an adverse effect.

- **Mechanism:** overstimulation of the mineralocorticoid receptor --> sodium retention in the kidney --> volume expansion.¹⁴
- Male sex may increase propensity to develop hypertension by increased RAAS (renin-angiotensin-aldosterone)¹⁵
- Renal dysfunction may increase risk of developing hypertension via poor salt excretion. Increased severity of tumor lysis can contribute to renal dysfunction.^{16,17}
- No current proposed mechanisms for BSA and hypertension risk.

Association of induction hypertension with steroid-induced hyperglycemia may suggest a patient-specific propensity to develop any steroid-related adverse effects.

- Despite increased incidence of hypertension in the AYA population, no long-term sequelae were found
- Hypertension may be protective for preventing conditions that require PICU admission.

Prospective cooperative group trials are needed to confirm these findings

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