Acute Limb Ischemia in a Cancer Patient Has High Morbidity, High Mortality, and Atypical Presentation: A Tertiary Cancer Center's Retrospective Study

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Abstract

Background

Acute Limb Ischemia (ALI) carries a high morbidity and mortality rate that is compounded in the cancer patient. Though it is a relatively uncommon event, it is of extremely high adverse impact and carries poor awareness among clinicians.

Methods

Cancer patients presenting with acute limb ischemia (ALI) to the tertiary cancer center's urgent care center or as inpatient between January 1, 2014 and January 1, 2020 were reviewed.

Results

Out of the 29 cancer patients with ALI, 12 (41%) died within 3 month and 9 (31%) patients died within 1 months of ALI diagnosis. 65% had long term adverse outcome after ALI – 31% with death in 1 month, 2 (7%) with an amputation, 5 (17%) with lifestyle-limiting claudication, and 3 (10%) with subsequent wound ulceration or gangrene. Patients not eligible for standard of care (12 patients, 41%) (RR 2.3333 95% CI [1.2743–4.2724], $p = 0.0022$) and heparin administration ≥ 6 hours from presentation (19 patients, 65%) (RR 2.8070 [1.0677–7.3795], $p = 0.0364$) were at increased risk of adverse outcome. Atypical/confounded presentation of ALI (13 patients, 45%) (RR 1.8367 95% CI [1.0266–3.2862], $p = 0.0405$), pulse exam not documented (12 patients, 41.4%) (RR 1.9479 [95% CI [1.1439–3.3169], $p = 0.0141$), and patients with services other than a vascular specialist initially consulted (8 patients, 27.6%) (RR 1.9091 95% CI [1.2698–2.8703], $p = 0.0019$) were significant risk factors for heparin administered ≥ 6 hours from presentation.

Conclusions

ALI is devastating in cancer patients, with a high number presenting with atypical/confounded signs and symptoms which delays treatment. Heparin administered ≥ 6 hours from presentation is associated with adverse outcome.

Background

Acute Limb Ischemia (ALI) is caused by sudden interruption of arterial blood flow to a limb (most often the lower extremity) threatening the viability of the limb, defined as acute (< 2 week), severe hypoperfusion of the limb characterized by pain, pallor, pulselessness, poikilothermia (cold), paresthesias, and paralysis.¹ It is usually caused by peripheral arterial disease (PAD) with in situ thrombosis or

embolus from a cardiac source due to arrhythmias like atrial fibrillation.^{1,2} The incidence is as high as 22–26 per 100,000 per year and carries a major amputation rate of 15–25% and mortality rate of 15–20% within the first year after the ALI event.¹ In the cancer patient, is a relatively uncommon event, but it is of extremely high adverse impact and carries poor awareness among clinicians, especially cancer specialists, with literature surrounding ALI in cancer patients compromised largely of case series and case reports. We present our experience at our tertiary cancer center's experience regarding presentation, risk factors, and outcome.

Methods

This single-institution tertiary cancer center retrospective study was approved by the Institutional Review Board. A Database inquiry of inpatient and urgent care center admission utilizing ICD 9/10 codes of 174.2 Embolism and Thrombosis of the upper extremities, 174.3 Embolism and thrombosis of arteries of the lower extremities, 174.5 Embolism and thrombosis of iliac artery, 174.5 Embolism and thrombosis of iliac artery, and 444.22 Lower extremity embolism from years January 1, 2014 to January 1, 2020 was performed. An electronic record review was done to assess demographics, cause of ALI, presentation, risk factors, treatment, time to anticoagulation and time to definitive treatment, type of treatment and outcome. Pulse examination (a critical component of the physical exam to assess for ALI) and whether other services were solicited before ALI was considered and referral made to a Vascular Specialist that treats ALI were also assessed.

Definitive treatment was described as final treatment decided upon – either watchful waiting as in patients who were not candidates for treatment, anticoagulation only therapy, endovascular procedure, or surgical procedure. Standard of care was defined as standard of care for ALI as recommended by 2016 AHA/ACC guidelines.^{5,6}

Hypercoagulable state as cause of ALI was described as thrombosis ≥ 2 noncontiguous vascular beds in the setting of Disseminated Intravascular Coagulation or progressed cancer with no other attributed cause for ALI. These patients were typically end stage, thrombocytopenic ($< 10,000$ platelets), and had sepsis or septic shock. Embolic cause was cardiac in source and due to an arrhythmia or heart failure. Some of these patients did however have underlying PAD that increased the propensity of ALI. PAD as a cause of ALI were patients who had pre-existing PAD with ALI due to in situ arterial thrombosis. Iatrogenic as cause of ALI was due to a surgical or interventional radiology procedure that involved a vascular bed.

Adverse outcome was classified as death within 1 month, amputation, lifestyle-limiting Rutherford 3 claudication, and critical limb ischemia (CLI). A table was constructed to reflect the clinical factors and outcomes between the no adverse outcome group and the adverse outcome group. Independent t-test and chi-squared test were used to identify any significant difference between both groups, as appropriate. Relative Risk analysis demonstrated any risk for death within 1 month and adverse outcome. Univariate and multivariate logistic regression modeling was used to assess prognostic variables for adverse outcome. Initiation of heparin ≥ 6 hours from presentation to the UCC or as inpatient was assessed as

one of the potential risk factors and prognostic variables. ≥ 6 hours was used as an extension of the 2016 AHA/ACC guidelines, where the 6 hour mark for ALI treatment is described.^{5,6} Statistical analyses were performed using MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2020). Significance was set at $p < 0.05$.

Results

29 patients met criteria for the study with mean age of 60 (± 14) years and median age of 61 years. 59% were men, 90% were white and 10% were Black. 83% were lower extremity ALI rather than upper extremity ALI. 8 (28%) were due to PAD, 7 (24%) were due to embolus from a cardiac source, 8 (28%) were iatrogenic from a procedure or surgery, and 6 (21%) were due to a hypercoagulable state. 18 (62%) patients had a threatened limb (Rutherford ALI 2a or 2b). Mean and median time to heparin drip was 17.5 hours (range 0.4-153.6 hours) and 8.6 hours, respectively. Mean and median time to definitive treatment was 23.8 hours (range 0.4-184.6 hours) and 8.6 hours, respectively. See Table 1.

Table 1

Summary of Demographics, Clinical Factors, and Outcome divided between the group with adverse outcome and the group with no adverse outcome.

	Adverse Outcome	No Adverse Outcome	Total	<i>P</i>
Number of patients	19, 65.5%	10, 34.5%	29	N/A
Age years Mean (SD)	61 (13)	57 (20)	60 (14)	0.4789
Age years (Median)	66	57	63	
Male	10, 52.6%	7, 70.0%	17, 58.6%	0.3743
White Race	16, 84.2%	10, 100.0%	26, 89.7%	0.1921
Black Race	3, 15.8%	0, 0.0%	3, 10.3%	0.1921
Genitourinary Cancer	3, 15.8%	3, 30.0%	6, 20.7%	0.3780
Gastrointestinal Cancer	5, 26.3%	4, 40.0%	9, 31.0%	0.4564
Gynecologic Cancer	1, 5.2%	0, 0.0%	1, 3.4%	0.4709
Breast Cancer	1, 5.2%	0, 0.0%	1, 3.4%	0.4709
Head and Neck Cancer	1, 5.2%	0, 0.0%	1, 3.4%	0.4709
Thoracic (lung, mesothelioma)	3, 15.8%	0, 0.0%	3, 10.3%	0.1921
Hematologic cancer	1, 5.2%	2, 20.0%	3, 10.3%	0.2208
Bone/soft tissue sarcoma	3, 15.8%	0, 0.0%	3, 10.3%	0.1921
Skin cancer	1, 5.2%	1, 10.0%	2, 6.9%	0.6328
Stage 1	3, 15.8%	4, 40.0%	7, 24.1%	0.1550
Stage 2	2, 10.5%	1, 10.0%	3, 10.3%	0.9670
Stage 3	3, 15.8%	0, 0.0%	3, 10.3%	0.1921
Stage 4	11, 57.9%	5, 50.0%	16, 55.2%	0.6895
Active chemotherapy	7, 36.8%	2, 20.0%	9, 31.0%	0.3610
Active prothrombotic chemotherapy	2, 10.5%	1, 10.0%	3, 10.3%	0.9670
Active immunotherapy	4, 21.1%	0, 0.0%	4, 13.8%	0.1242
Active radiation therapy	2, 10.5%	0, 0.0%	2, 6.9%	0.2968
Clonal Hematopoiesis of Indeterminate Potential	1, 5.2%	1, 10.0%	2, 6.9%	0.6328
Diabetes	6, 31.5%	4, 40.0%	10, 34.5%	0.6528

	Adverse Outcome	No Adverse Outcome	Total	<i>P</i>
Hypertension	11, 57.9%	7, 70.0%	18, 62.1%	0.5305
Hyperlipidemia	6, 31.5%	4, 40.0%	10, 34.5%	0.6528
Chronic kidney disease	5, 26.3%	2, 20.0%	7, 24.1%	0.7111
Coronary artery disease	7, 36.8%	1, 10.0%	8, 27.6%	0.1314
Cerebrovascular disease	0, 0.0%	0, 0.0%	0, 0.0%	—
Peripheral arterial disease	7, 36.8%	3, 30.0%	10, 34.5%	0.7189
Obesity	5, 26.3%	3, 30.0%	8, 27.6%	0.8350
Atrial fibrillation or other cardiac dysarrhythmia	6, 31.5%	0, 0.0%	6, 20.7%	0.0503
Smoking	7, 36.8%	5, 50.0%	12, 41.4%	0.4803
Anti-platelet therapy	5, 26.3%	1, 10.0%	6, 20.7%	0.3114
Statin therapy	2, 10.5%	2, 20.0%	4, 13.8%	0.4881
Anticoagulation therapy	3, 15.8%	0, 0.0%	3, 10.3%	0.1921
Anticoagulation indicated but held/not taken leading up to ALI	7, 36.8%	0, 0.0%	7, 24.1%	0.0305
Lower extremity ALI (verses upper extremity) n, %	16, 84.2%	8, 80.0%	24, 82.8%	0.7798
Cause of ALI: Embolic n, %	6, 31.6%	1, 10.0%	7, 24.1%	0.2043
Cause of ALI: Hypercoaguable State n, %	5, 26.3%	1, 10.0%	6, 20.7%	0.3114
Cause of ALI: Iatrogenic n, %	3, 15.8%	5, 50.0%	8, 27.6%	0.0543
Cause of ALI: PAD n, %	5, 26.3%	3, 30.0%	8, 27.6%	0.8350
Threatened limb (Rutherford ALI 2a and 2b)	13, 68.4%	5, 50.0%	18, 62.1%	0.3402
Atypical or confounded presentation, n, %	9, 47.4%	4, 40.0%	13, 44.8%	0.7082
Pulses NOT documented	9, 47.4%	3, 30.0%	12, 41.4%	0.3743
Patients with services other than vascular specialist consulted	7, 36.8%	1, 10.0%	8, 27.6%	0.1314
Time to Heparin intravenous (initial treatment) Hours Mean (SD), range	23.6 (39.4), 1.0-153.6	5.9 (6.8), 0.4-20.4	17.5 (33.8), 0.4-153.6	0.1845

	Adverse Outcome	No Adverse Outcome	Total	<i>P</i>
Time to Heparin intravenous (initial treatment) Hours Median	10.1	2.4	8.6	—
Time to Definitive treatment Hours Mean (SD), range	23.0 (39.7), 1.0-153.6	25.1 (55.9), 0.4-184.6	23.8 (45.8), 0.4–184.6	0.9112
Time to Definitive treatment Hours Median	8.8	5.5	8.6	—
Heparin initiated $\geq$ 6 hours from presentation	16, 84.2%	3, 30.0%	19, 65.5%	0.0041
NOT eligible for ALI Standard of Care n, %	12, 63.2%	0, 0.0%	12, 41.4%	0.0013
Death in follow up period n, %	12, 63.2%	1, 10.0%	13, 44.8%	0.0071
Death in 3 months n, %	12, 63.2%	0, 0.0%	12, 41.4%	0.0013
Death within 1 month n, %	9, 47.4%	N/A	9, 31.0%	N/A
ALI-related cause of death n, %	6, 31.6%	N/A	6, 46.1%	N/A
Cancer-related cause of death n, %	4, 21.1%	1, 10.0%	5, 38.4%	0.4602
Cardiac arrest from Myocardial Infarction as cause of death n, %	2, 10.5%	0, 0.0%	2, 15.4%	0.2968
Amputation n, %	2, 10.5%	N/A	2, 6.8%	N/A
Lifestyle-limiting claudication n, %	5, 26.3%	N/A	5, 17.2%	N/A
Critical limb ischemia, n, %	3, 15.8%	N/A	3, 10.3%	N/A
Mean (SD) Follow up, months	6 (14)	24 (15)	12 (17)	0.0075
Median Follow up, months	2	21	3	—

Mean follow up for the entire cohort was 12 months $\pm$ 17 months, with median follow up of 3 months. In the follow up period 13 (45%) patients died, with 12 (41%) patients dying within 3 months of ALI diagnosis and 9 (31%) dying within 1 month of ALI diagnosis. Immediate causes of death were ALI-related (6, 46%), cancer-related (5, 38%), and cardiac arrest from a Myocardial Infarction (2, 15%). See Table 1.

Out of all 29 patients, only 9 (31%) were alive without adverse outcome in the follow up period. One patient died within the study period from cancer and did not have adverse ALI outcome. Those with classified adverse outcome (19, 65%) included – 9 (31%) dying within 30 days, 2 (7%) with an amputation, 5 (17%) with lifestyle-limiting claudication, and 3 (10%) with critical limb ischemia with wound ulceration or gangrene (Table 1).

Between the group with adverse outcome and the group with no adverse outcome, there were statistically significant differences in number of patients with anticoagulation being held/not taken leading up to ALI (adverse outcome group 36.8% vs no adverse outcome group 0.0%, $p = 0.0305$), heparin being administered ≥ 6 hours from presentation (adverse outcome group 84.2% vs no adverse outcome group 30.0%, $p = 0.0041$), number of patients not eligible for standard of care (adverse outcome group 63.2% vs. no adverse outcome group 0.0%, $p = 0.0013$), death in the follow up period (adverse outcome group 63.2% vs. no adverse outcome 10.0%, $p = 0.0071$), and death within 3 months (adverse outcome group 63.2% vs. no adverse outcome 0.0%, $p = 0.0013$). Follow up was shorter in the adverse outcome group compared to the no adverse outcome group (6 months vs. 24 months, $p = 0.0075$) consistent with the large amount of deaths in the adverse outcome group. All other factors (outside the definition of adverse outcome), including type of cancer, stage of cancer, cancer therapy, prothrombotic chemotherapy, comorbidities, the use of antiplatelet therapy, statin therapy, or anticoagulation were not statistically different between both groups. See Table 1.

Patients with hypercoagulable state were at increased risk of death within 1 month (RR 3.0667 95% CI [1.1743–8.0085], $p = 0.0221$). Patients NOT eligible for standard of care (RR 2.3333 95% CI [1.2743–4.2724], $p = 0.0022$) and heparin administration ≥ 6 hours (RR 2.8070 [1.0677–7.3795], $p = 0.0364$) from presentation were at increased risk of adverse outcome.

In univariate analysis, Heparin started ≥ 6 hours from presentation was a predictor for adverse outcome with 12 times greater odds for adverse outcome than patients with heparin administered < 6 hours (OR 12.4444 [95% CI 1.996–77.600], $p = 0.0069$) (Table 2). Atypical or confounded presentation (RR 1.8367 95% CI [1.0266–3.2862], $p = 0.0405$), pulse exam not documented (RR 1.9479 [95% CI [1.1439–3.3169], $p = 0.0141$), and services other than a vascular specialist consulted, (RR 1.9091 95% CI [1.2698–2.8703], $p = 0.0019$) were significant risk factors for heparin started ≥ 6 hours from presentation (Table 3).

Table 2
Prognostic variables for adverse outcome in a logistic regression model.

	OR	95% CI	<i>P</i> (univariate)	<i>P</i> (multivariate)
Cause of ALI: Embolus	4.1538	0.4243– 40.6627	0.2211	
Cause of ALI: Hypercoaguable state	3.2143	0.3208– 32.2076	0.3207	
Cause of ALI: Iatrogenic	0.1875	0.0326–1.0774	0.0606	
Cause of ALI: PAD	0.8333	0.1530–4.5376	0.8330	
Threatened Limb	2.1667	0.4497– 10.4393	0.3352	
Not eligible for ALI standard of care	35.0000	1.7813– 687.7111	0.9980	
Heparin administration ≥ 6 hours	12.4444	1.996–77.600	0.0069	0.9984

Table 3
Risk and significance of variables leading to administration of heparin ≥ 6 hours from presentation.

	Relative Risk	95% CI	<i>P</i>
Atypical or confounded presentation	1.8367	1.0266–3.2862	0.0405
Pulse not documented	1.9479	1.1439–3.3169	0.0141
Other services consulted	1.9091	1.2698–2.8703	0.0019

In the studied population, only 16 (55%) of patients had a typical presentation of ALI (Table 1). The other 13 (45%) patients presented with confounding signs and symptoms such as cancer-related pain such as back and radicular pain from retroperitoneal and spine metastatic involvement (4, one patient also with unrelated rash in the ipsilateral limb), post-surgical pain (2, one patient also with unrelated cellulitis in the ipsilateral limb), unrelated fever with pneumonia (1), unrelated severe shortness of breath from pulmonary embolus or CHF exacerbation (2), generalized weakness and dizziness due to advanced disease state/failure to thrive (1), unable to communicate symptoms due to unconsciousness (1), and small bowel obstruction with nausea/vomiting resulting in hypovolemia and arterial thrombosis in the setting of PAD (2).

12 (41%) patients did not have pulse exam documented at the time of presentation. In addition, 8 (28%) patients had referrals placed to other services such as Neurology, Pain, or Rheumatology Service before the diagnosis of ALI was considered and referral placed for a Vascular Specialist with the ability to treat ALI. See Table 1.

Discussion

ALI is a devastating event with an extremely poor prognosis. It has a reported mortality rate of 15–20% within one year of the event, due to concomitant illness such as cardiovascular or cerebrovascular disease and ischemia–reperfusion injury.^{1,5} ALI may be compounded by cancer factors that worsen the outcome of ALI or prohibit standard of care for ALI. This study in cancer patients demonstrated a 3-month mortality rate of 41% and a 1-month mortality of 31% which is higher than reported values in the general population.^{1,5} ALI has a high mortality, but is also an extremely morbid disease with less than one-third of the cancer patients being alive and without long-term adverse outcome in the follow up period. 65% of the patients had an adverse outcome – death within 1 month (with hypercoagulable state being at increased risk for death within 1 month), amputation, lifestyle-limiting claudication, or critical limb ischemia.

In this study, ALI was caused by PAD, embolus from a cardiac source, iatrogenic from procedure/surgery, and hypercoagulable state. Moreover, there were patients that had anticoagulation prescribed (typically in the setting of atrial fibrillation) but not taken either due to treatment related thrombocytopenia, pending cancer surgery/procedure, or noncompliance that resulted in ALI and was significantly overrepresented in the adverse outcome group.

41% of the patients did not have pulse exam documented in the setting of ALI and 28% had services consulted other than a vascular specialist at the time of ALI presentation. This may be because of lack of awareness among clinicians as has been repeatedly described in the literature when discussing findings associated with ALI in the general population.^{7,8,9,10,11} However, this may also be because so many cancer patients do not present with the typical presentation that occurs in the general population. Therefore, the oncologist's awareness and heightened suspicion for ALI may be helpful even in the setting of atypical/confounded presentation to mitigate delay so appropriate exam is performed and referral to a vascular specialist is made. Early diagnosis and prompt initiation of therapy are essential to avoiding an adverse outcome.¹² In this study, initiation of treatment ≥ 6 hours from presentation was predictive of an adverse outcome.

Prognosis of ALI patients is also dependent on appropriate treatment.^{13,14,15,16} The Consensus by the American Heart Association/American College of Cardiologists recommends that marginally or immediately threatened limbs (Rutherford ALI 2a and 2b), should be revascularized emergently (within 6 hours) and viable limbs (Rutherford ALI 1), should be revascularized on an urgent basis (within 6–24 hours). The revascularization strategy ranges from catheter-directed thrombolysis to surgical thromboembolectomy. Systemic anticoagulation with intravenous heparin should be administered upon presentation to improve outcome.⁶ However, 41% of the cancer patients in this study were not eligible to receive ALI standard of care due to poor procedure or anticoagulation candidacy due to cancer or cancer therapy complications. All patients not able to receive ALI standard of care were in the adverse outcome group. Patients not eligible for ALI standard of care had two times the risk of adverse outcome.

Conclusions

ALI is a devastating event especially in a cancer population, carrying an extremely high morbidity and mortality, with less than one-third of the cancer patients in this study alive and without adverse outcome in the follow up period. 45% of the cancer patients had an atypical or confounded ALI presentation delaying diagnosis. Initiation of heparin ≥ 6 hours from presentation was predictive of adverse outcome. Moreover, 41% of the cancer patients in this study were not able to receive standard of care for ALI with increased risk of adverse outcome.

Abbreviations

ALI: Acute Limb Ischemia

PAD: Peripheral Arterial Disease

UCC: Urgent Care Center

ICD: International Classification of Disease

RR: Relative Risk

AHA: American Heart Association

ACC: American College of Cardiology

CLI: Critical Limb Ischemia

SD: Standard Deviation

Declarations

Ethics approval and consent to participate: Ethics approval was obtained from our institution the Memorial Sloan Kettering Cancer Center Institutional Review Board (IRB) with need for consent waived in accordance to the Declaration of Helsinki.

Consent for publication: Individual consent for publication was not obtained as individual details, images, or videos were not utilized.

Availability of data and materials: The minimal dataset that is necessary to interpret, replicate, and build upon findings are available from the corresponding author on reasonable request

Competing interests: Dr. Etay Ziv, MD, PhD has the following grants - AACR, SIR, RSNA, NANETS, Druckenmiller, MSK Society, MSK FGI, MSK Radiology Seed, Ethicon, Novartis, none of which are of

competing interest for this study. The remainder of the authors do not have any potential competing interest to disclose.

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Authors' contributions: YB was involved in conceptualization, methodology, formal analysis, investigation, data curation, writing the original draft, writing the review and editing, and visualization. EA was involved in conceptualization and writing the review and editing. CA, CH, and SH were involved in resources and writing the review and editing. EZ was involved in conceptualization, writing the review and editing, and visualization. ES was involved in conceptualization, writing the review and editing, visualization, and supervision.

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