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Age does not predict need for reintervention in patients with critical limb ischemia

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Objective: **Conventional wisdom holds that patients with a need for intervention for femoropopliteal occlusive disease at a younger age have more aggressive disease, although there is a paucity of support in the literature. The purpose of this study was to evaluate this assumption.**

Methods: **A retrospective cohort of patients undergoing endovascular or open revascularization for femoropopliteal occlusive disease for critical limb ischemia during a 4-year period was assembled. Demographic information, comorbidities, disease characteristics, and time to last follow-up, repeat intervention, amputation, or death was recorded. The patients were stratified by age into a young (≤55 years) group, middle (56-77 years) group, and elderly (≥78 years) group. Univariate and multivariate statistical methods were used to evaluate the primary outcome.**

Results: **The study included 124 patients with a mean age of 64.4 ± 0.8 years. Progression to reintervention or amputation occurred in 50% of the patients during the follow-up period, with 18% dying before having an outcome. Kaplan-Meier analysis showed a trend toward significance ($P = .06$) in time to reintervention, amputation, or death among the three groups, with time to event of 253, 1083, and 504 days for the young, middle, and elderly groups, respectively. However, differences based on age were not significant ($P = .57$) in Cox regression analysis.**

Conclusions: **There does not appear to be an association between time to reintervention and patient age. (J Vasc Surg 2015;61:413-8.)**

Peripheral arterial disease (PAD) is often associated with increasing age. Estimates are that 10% of people aged >65 years and 20% aged >75 years in the Western world have this disease process.[1] PAD can also be seen in younger patients, however, with up to 28% of PAD patients aged <65 years.[2] Onset at an age of <50 years is defined as premature.[3] Some believe that those with younger age at onset have a more aggressive atherosclerotic disease process.[4]

Despite conventional wisdom that patients presenting with PAD at a younger age have a more aggressive disease process, there is scant supporting evidence in the literature. The objective of this study was to investigate the relationship between age and progression to reintervention or amputation after intervention for femoropopliteal occlusive disease.

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METHODS

In this retrospective study, a cohort of all patients undergoing an open or endovascular intervention for critical limb ischemia secondary to femoropopliteal occlusive disease from July 2003 through July 2006 was identified by Common Procedural Terminology codes (American Medical Association, Chicago, Ill), and a database was constructed with Institutional Review Board approval. As a retrospective study, informed consent was not obtained because patients were not placed at risk and many were lost to follow-up or had died. The decision for an open or endovascular intervention had been determined according to clinical evaluation, anatomic factors, and surgeon preference. The medical record for each patient was reviewed to record demographics, preoperative factors, procedural factors, and outcomes.

Comorbid conditions and smoking status were also recorded. The comorbidities were defined as diabetes (by medical treatment), hypertension (by medical treatment), hyperlipidemia (by medical treatment or total cholesterol >200 mg/dL), tobacco use (lifetime and current use), coronary disease (by medical treatment or history of coronary intervention), renal insufficiency (by creatinine >1.5 mg/dL), and end-stage renal disease (ESRD; by renal failure with chronic renal replacement therapy).

The record was reviewed for the end points of death, endovascular or open reintervention on the index extremity, amputation, or the end of the follow-up period in August 2013.

The population was divided into the oldest quartile, youngest quartile, and a final group consisting of the

middle two quartiles. Univariate statistical methods were used to define general population characteristics and characteristics of the individual age groups.

Because of the small size of the sample, a power analysis was undertaken. Kaplan-Meier survival analyses were performed for the overall group and for the individual age groups. The end point for these analyses was time to reintervention or amputation. Patients who were lost to follow-up or did not reach either end point at the time of termination of follow-up were censored. Because of a higher rate of death expected in the elderly group, this analysis was inherently biased because of the strong possibility of shorter follow-up times in this group. For this reason, a separate analysis was done with reintervention, amputation, or death as the end point.

Cox regression analysis was performed for Kaplan-Meier survival curves with $P \leq .20$, with time to reintervention or amputation as the end point to further investigate the link between age group and primary outcomes when controlling for possible confounders. A separate analysis was done using reintervention, amputation, or death as the end point because of the possible confounding effect of a higher death rate in the elderly patients. All potential confounders from our data were included in the original model, and stepwise backwards selection was used to arrive at the final model.

Table I. Overall population demographics, disease at presentation, comorbidities, and outcomes

Variable	*Mean ± SE,[a] No. (%), or median (95% CI)*
Age, years	66.5 ± 1.2
Age groups, years	
≤55	32 (26)
56-76	60 (48)
≥78	32 (26)
Female	62 (50)
Diabetes mellitus	
Insulin-dependent	14 (11)
Noninsulin-dependent	49 (40)
Hypertension	94 (76)
Hyperlipidemia	55 (44)
Smoker	66 (53)
Former smoker	24 (19)
ESRD	19 (15)
CAD	50 (40)
Congestive heart failure	37 (30)
Open procedure	90 (73)
Reintervention or amputation	68 (55)
Death before outcome	23 (19)
Time to outcome or death, months	10 (6.3-20.9)

CAD, Coronary artery disease; *CI,* confidence interval; *ESRD,* end-stage renal disease; *SE,* standard error.
[a]Except as noted for time to outcome or death.

RESULTS

The study population included 124 patients with a mean age of 66.5 ± 1.2 years. The mean follow-up time was 22.6 ± 2.7 months. Noninsulin-dependent diabetes mellitus was present in 40%, and insulin-dependent diabetes mellitus was present in 11%. Progression to repeat intervention occurred in 55% of patients, and 19% died before having an outcome. Table I summarizes the overall population characteristics.

Table II reports the demographics, comorbidities, and outcomes for the different groups. There were significant differences in gender ($P = .03$), smoking ($P = .0005$), congestive heart failure ($P = .02$), and death before an event happened ($P = .03$).

Based on a sample size of 124 patients, a standard error of 32, and an α of .05, the power of this study was 0.720.

The young group (age ≤55 years; n = 32) was a mean age of 48.9 ± 1.0 years. Of these, 38% were women, 9.4% had quit smoking, 8% had an open procedure. Progression to reintervention or amputation occurred in 69%, and 6% died before an outcome occurred.

The middle group (age 56-77 years; n = 60) was a mean age of 66.6 ± 0.7 years. Former smokers made up 23% of this group, and 75% had an open procedure. Progression to reintervention or amputation occurred in 55%, and 18% died before reaching an outcome.

The elderly group (age ≥78 years; n = 32) was a mean age of 83.7 ± 1.0 years. Women made up 68.8% of this group, 22% were former smokers, and 63% had an open procedure. Progression to reintervention or amputation occurred in 41%, and 31% died before reaching an outcome.

Kaplan-Meier survival analysis for time to reintervention or amputation (Fig 1) showed no significant difference among groups ($P = .23$), with median times to reintervention or amputation of 8.3 months for the young group and 15.9 months for middle group. The elderly group did not have a median time because <50% had an outcome due mostly to 31% having died during follow-up before having an event.

The Kaplan-Meier survival analysis for reintervention, amputation, or death (Fig 2) showed no significant difference among the age groups ($P = .97$). Median time to reintervention, amputation, or death was 301 days. Median times to intervention or death for the young, middle, and elderly groups were 5.1, 11.6, and 10.0 months, respectively.

To ensure that the group meeting the criteria for premature PAD within the young group was not significantly different from the group that did not, the number of events and the time to events were examined for these two groups. There were 16 (50%) patients in this group meeting criteria for premature PAD. For both groups, 31% progressed to reintervention or amputation ($P = 1.00$). Death before an event occurred in 6% of both groups ($P = 1.00$). On Kaplan-Meier analyses, there were no significant differences in time to reintervention or amputation ($P = .46$), or reintervention, amputation, or death ($P = .45$) between the premature PAD patients and the rest of the young group.

On Cox regression for reintervention or amputation, age group was not a significant factor ($P = .25$) when controlling for potential confounders (Table III). Quitting smoking was protective against progression (relative risk

Table II. Demographics, disease at presentation, comorbidities, and outcomes by age group

Variable[a]	*Young (n = 32)*	*Middle (n = 60)*	*Elderly (n = 32)*	P
Age, years	48.9 ± 1.0	66.6 ± 0.7	83.3 ± 1.0	<.0001
Female	12 (38)	28 (47)	22 (68.8)	.03
Diabetes mellitus				
Insulin dependent	3 (9)	7 (12)	4 (13)	.92
Noninsulin dependent	15 (47)	26 (43)	8 (25)	.13
Hypertension	23 (72)	47 (78)	24 (75)	.78
Hyperlipidemia	17 (53)	28 (47)	10 (31)	.18
Smoker	18 (52)	40 (67)	8 (25)	.005
Former smoker	3 (9)	14 (23)	7 (22)	.21
ESRD	7 (22)	11 (19)	1 (3)	.0.04
CAD	17 (53)	21 (35)	12 (38)	.23
Congestive heart failure	5 (16)	17 (28)	15 (47)	.02
Open procedure	25 (78)	45 (75)	20 (63)	.33
Reintervention or amputation	22 (69)	33 (55)	13 (41)	.08
Death before event	2 (6)	11 (18)	10 (31)	.03
Time to death or event, months	5.1 (3.8-26.0)	11.6 (7.7-32.7)	10.0 (2.8-40.8)	.97

CAD, Coronary artery disease; *CI,* confidence interval; *ESRD,* end-stage renal disease; *SE,* standard error.
[a]Continuous variables are shown as mean ± SE or median (95% CI) and categorical variables as number (%).

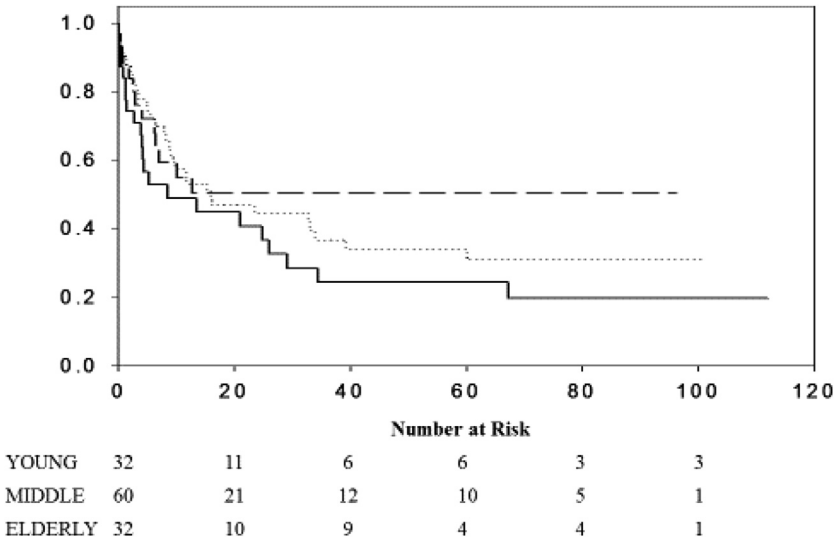

Fig 1. Kaplan-Meier survival curves for time to reintervention or amputation for young (*solid line*), middle (*dotted line*), and elderly (*dashed line*) patients ($P = .23$).

[RR], 0.46; 95% confidence interval [CI], 0.21-0.91). Having an open procedure strongly trended toward significance (RR, 0.60; 95% CI, 0.35-1.03). ESRD was associated with progression to the primary end points (RR, 2.56; 95% CI, 1.29-4.86). Coronary artery disease (CAD) was also associated with a decreased likelihood of progression of disease (RR, 0.44; 95% CI, 0.25-0.76). Those with CAD were more likely to have died before reaching an event ($P = .07$): 30% of patients with CAD compared with 10% without CAD died before having an outcome.

On Cox regression for reintervention, amputation, or death, age group was not a significant factor ($P = .97$) when controlling for potential confounders (Table IV). An open procedure was associated with a decreased risk of progression (RR, 0.58; 95% CI, 0.36-0.93). Having quit smoking was also protective (RR, 0.53; 95% CI, 0.29-0.91). ESRD was associated with increased risk of progression (RR, 2.48; 95% CI, 1.38-4.26). Gender and quitting smoking were not significant but neared significance and remained in the model.

DISCUSSION

Early onset of PAD symptoms is often assumed to be attributable to an accelerated atherosclerotic process.[5] That patients presenting at younger ages go on to require more interventions has also been noted.[4] Going along with this, a study of patients aged <45 years found that 41%

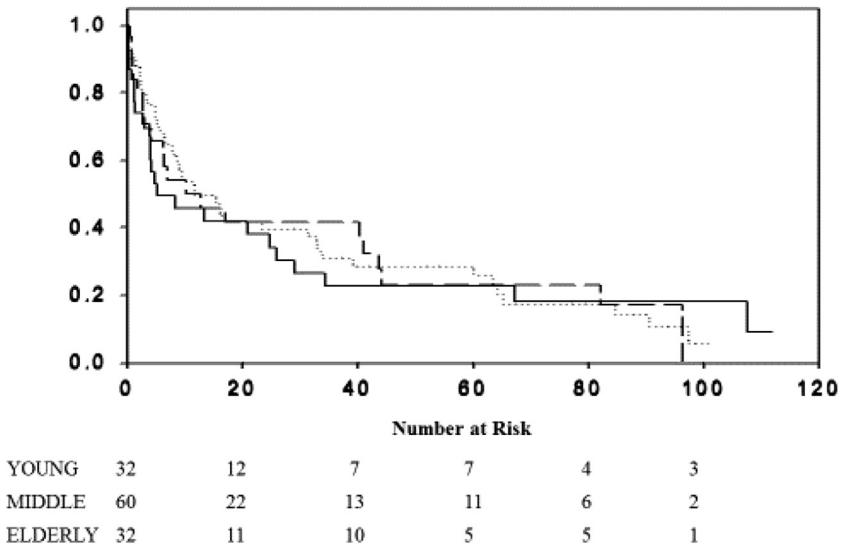

Fig 2. Kaplan-Meier survival curves for time to reintervention, amputation, or death for young (*solid line*), middle (*dotted line*), and elderly (*dashed line*) patients ($P = .97$).

Table III. Cox regression for risk of progression to reintervention or amputation ($P = .0005$)

Variable	*RR*	*95% CI*	P
Age group, years			.25
≤55 vs 56-77	1.63	0.90-2.90	
≤55 vs ≥78	1.57	0.77-3.34	
CAD	0.44	0.25-0.76	.003
Former smoker	0.46	0.21-0.91	.02
ESRD	2.56	1.29-4.86	.008
Open procedure	0.60	0.35-1.03	.06

CI, Confidence interval; *CAD,* coronary artery disease; *ESRD,* end-stage renal disease; *RR,* relative risk.

Table IV. Cox regression for risk of progression to reintervention, amputation, or death ($P = .0007$)

Variable	*RR*	*95% CI*	P
Age group, years			.97
≤55 vs 56-77	0.97	0.57-1.61	
≤55 vs ≥78	0.93	0.49-1.75	
Smoker	0.67	0.42-1.09	.11
Former smoker	0.53	0.29-0.91	.02
ESRD	2.48	1.38-4.26	.003
Open procedure	0.58	0.36-0.93	.03

CI, Confidence interval; *ESRD,* end-stage renal disease; *RR,* relative risk.

eventually required repeated interventions or amputations for progression of their disease or graft failure.[3]

There is evidence that patients presenting with premature PAD can go on to poor outcomes. Repeated atheroembolic events and lack of collaterals have been noted to sometimes lead to rapid deterioration toward critical limb ischemia in the population.[6] Early bypass failure and amputation have also been reported.[3] Other studies have looked into potential causes, with a series of 51 patients with premature PAD finding that 90% had laboratory abnormalities.[7]

As with these studies, we also found poor outcomes in the young population. With a mean age of 48.9 ± 1.0 years, our young group was largely in the range of premature PAD. Half of this group met criteria for premature PAD. Within the young group, comparing those who did and did not meet criteria for premature PAD (age ≥50) found no differences in reintervention or amputation, death before reintervention, or death. There was also no difference in time to event on either analysis. In the 10 years of follow-up from initiation of the record review, 6% had died and 66% progressed to reintervention or amputation after the initial intervention. However, unlike the prior listed studies, we were able to compare this group with older groups. The incidence of death during the time frame of this study was significantly higher in the elderly group (31%).

We used the time frame of 2003 to 2006 to draw our patient sample from to allow ∼10 years of follow-up. The mean follow-up time was ∼2.5 years, which was largely related to many of the events occurring within that time frame. In addition, with the advancement of endovascular techniques in later years, this would have added to the potential for a more heterogeneous sample and confounding.

Death is a potential confounder. Death removes a larger subset of the older individuals from the at-risk pool. When death was controlled for in the Kaplan-Meier survival analysis, there was no significant difference among the groups.

Open procedures have been associated with longer patency.[8] Our data support this, with a significant result on the Cox regression analysis that included death and a strong trend toward significance on the other. The

inclusion of open and endovascular procedures in the analysis has the potential to confound our results, because the failure modes for endovascular and open procedures are different. However, univariate analysis found no association among the age groups and the procedure type ($P = .33$). This issue was further controlled for on multivariate analysis. Because of the number of individuals involved, breaking down the analysis into endovascular and open groups would result in too small a sample to analyze. On the basis of the design of our study, comparing if failure across groups was related to atherosclerotic progression or intimal hyperplasia was not possible.

A study by Harris et al[9] found similar results in elevated poor overall outcome rates in the younger population. They had 76 patients with premature PAD and 76 patients aged >60 years matched for disease distribution and found an increased prevalence of late amputations in the study group compared with the control group (26% vs 1.73%; $P < .0001$). However, it should be noted that the follow-up times were 62 ± 48 months for the study group and 33.4 ± 27 months for the control group.[9]

Our univariate analysis showed a higher proportion of patients in the young group progressed to reintervention or amputation compared with the other two groups. This was not statistically significant ($P = .08$), although it does strongly trend in that direction. This was offset by the fact that higher proportions of individuals in the two older groups died before having an outcome ($P = .03$). When reintervention, amputation, and death are taken into account in the Kaplan-Meier analysis, there is no difference among groups ($P = .97$).

As in the Harris et al[10] study, we found an increased prevalence of female patients in the older group. PAD is not as prevalent in premenopausal women, but after menopause, the prevalence increases and is similar to the prevalence in men.[10] This is similar to what occurs in our data and is concerning because prior research has shown that female gender is an independent risk factor for amputation.[11] However, other studies have shown no significant difference between men and women in outcomes.[12] In our data, gender had no effect on the primary outcomes, and this variable was not significant in the Cox regression model.

If premature PAD in our population does not progress more rapidly after the initial procedure, then the question is raised why these patients are developing disease at a young age. This may be related to other risk factors. Our young and middle groups were more likely to be smokers than the elderly group; in addition, the young group was the least likely to have quit smoking. Our young group was the most likely to have ESRD. Smoking and ESRD are well-known risk factors for disease progression.[13,14]

It is interesting that CAD appeared to be a protective factor for disease progression in the Cox model only taking into account reintervention and amputation as the end point. CAD disappears a significant factor when death is taken into account. On closer analysis, CAD appears to be a marker of patients more likely to die before reaching reintervention or amputation. Almost one in three of the patients with CAD compared with only one in 10 without CAD died before reaching an outcome.

The possibility exists that there are subsets of patients with premature PAD who will progress; however, that was beyond the scope of this study. In addition, that possibility holds true across age groups.

Our sample was limited to patients with femoropopliteal disease, which is a potential limitation to this study. This facilitated comparison of a more homogenous population with similar lesions. However, this excludes the possibility of studying multilevel disease and whether prevalence is associated with age and its relationship with our end points.

CONCLUSIONS

Patients presenting with symptomatic PAD at a younger age are commonly assumed to represent a population with more aggressive disease; however, age was not an independent risk factor for disease progression after the first intervention. The higher prevalence of repeat interventions and progression to amputation in younger patients are more likely related to a longer lifespan compared with the older group. In addition, the young age at presentation may relate to other risk factors.

AUTHOR CONTRIBUTIONS

Conception and design: DT, MS
Analysis and interpretation: DT, JZ, WB, CP, FP, DY, MS
Data collection: DT, JZ, WM, CP, FP, DY, MS
Writing the article: DT
Critical revision of the article: DT, JZ, WB, CP, FP, DY, MS
Final approval of the article: DT, JZ, WB, CP, FP, DY, MS
Statistical analysis: DT, MS
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Overall responsibility: MS

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