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Original Contributions

DIAGNOSTIC ACCURACY AND FINANCIAL IMPLICATIONS OF AGE-ADJUSTED D-DIMER STRATEGIES FOR THE DIAGNOSIS OF DEEP VENOUS THROMBOSIS IN THE EMERGENCY DEPARTMENT

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☐ **Abstract—Background: Multiple D-dimer cutoffs have been suggested for older patients to improve diagnostic specificity for venous thromboembolism. These approaches are better established for pulmonary embolism. Objectives: We evaluated the diagnostic performance and compared the health system cost for previously suggested cutoffs and a new D-dimer cutoff for low-risk emergency department (ED) deep venous thrombosis (DVT) patients. Methods: We conducted a retrospective cohort study in two large EDs involving patients aged > 50 years who had low pretest probability for DVT and had a D-dimer performed. The outcome was a diagnosis of DVT at 30 days. We evaluated the diagnostic accuracy and estimated the difference in cost for cutoffs of 500 ng/mL and the age-adjusted (age × 10) rule. A derived cutoff of 1000 ng/mL was also assessed. Results: Nine hundred and seventy-two patients were included (median age 66 years; 59.5% female); 63 (6.5%) patients were diagnosed with DVT. The conventional cutoff of < 500 ng/mL demonstrated a sensitivity of 100% (95% confidence interval [CI] 94.3–100%) and a specificity of 35.6% (95% CI 32.5–38.8%). The age-adjusted approach increased specificity while maintaining high sensitivity. A new cutoff of 1000 ng/mL demonstrated improved performance: sensitivity 100% (95% CI 94.3–00%) and specificity 66.3% (95% CI 63.2–69.4%). Compared to the conventional approach, both the 1000 ng/mL cutoff and the age-adjusted cutoffs could save healthcare dollars. A cutoff of 1000 ng/mL could have saved 310 ED length of stay hours and $166,909 (Canadian dollars) in our cohort, or an average savings of 0.32 h and $172 per patient. Conclusions: Among patients aged > 50 years with suspected DVT, the age-adjusted D-dimer and a cutoff of 1000 ng/mL improved specificity without compromising sensitivity, and lowered the health care system cost compared to that for the conventional approach.**

☐ **Keywords—D-dimer; deep venous thrombosis**

INTRODUCTION

Venous thromboembolism incidence rises incrementally with age, approaching an annual rate of 0.5% in those aged > 80 years (1,2). D-dimer values increase similarly, reducing the specificity of D-dimer rule-out algorithms in elderly patients (3–8). Only 5% of patients

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aged > 80 years of age will have a D-dimer below the conventional cutoff of 500 ng/mL (3,8). This reduces the cost effectiveness of D-dimer use in elderly patients, and also leads to harm through unnecessary investigations, anticoagulation, and anxiety incurred from incidental diagnoses.

To improve specificity of rule-out algorithms, a variety of age-adjusted cutoffs have been suggested for older patients. Using receiver operating characteristic (ROC) curves, Harper et al. identified a modified cutoff of 1000 ng/mL for patients suspected of venous thromboembolism, which increased specificity from 5% to 27% in patients aged > 80 years, while maintaining a sensitivity of > 98% for patients aged > 60 years (3). Douma et al. developed the age-adjusted D-dimer rule (age × 10), which resulted in 5–6% more negative D-dimers compared to the conventional cutoff in patients with suspected pulmonary embolism (PE) (9). The safety of this approach has been demonstrated in other studies (10). A similar approach for developing a D-dimer cutoff using ROC curves has not been performed in patients with suspected DVT.

Righini and colleagues prospectively validated the age-adjusted D-dimer rule, demonstrating an 11.6% increase in the proportion of negative D-dimer results using the age-adjusted rule in the workup of PE (11). Retrospective studies have been performed in suspected DVT, but with more modest results (3,12–16). However, there is still a considerable economic impact from these strategies. A retrospective application of the age-adjusted D-dimer in a French cohort suggested an 11% decrease in overall costs associated with workup for patients with suspected PE and 6.3% for DVT (17).

Importance

There is no consensus regarding the best approach to D-dimer interpretation in suspected DVT. There is also a paucity of studies examining the financial implications of these approaches or diagnostic performance in the North American ED population. This study will evaluate and compare the diagnostic performance and the difference in costs of previously suggested D-dimer cutoffs for patients with low pretest probability of DVT patients in the ED. We will also assess whether a novel cutoff with improved performance can be identified.

METHODS

Study Design

This study was a health records review of patients presenting to the ED with suspected DVT. The study was conducted with approval of The Ottawa Health Science Network Research Ethics Board.

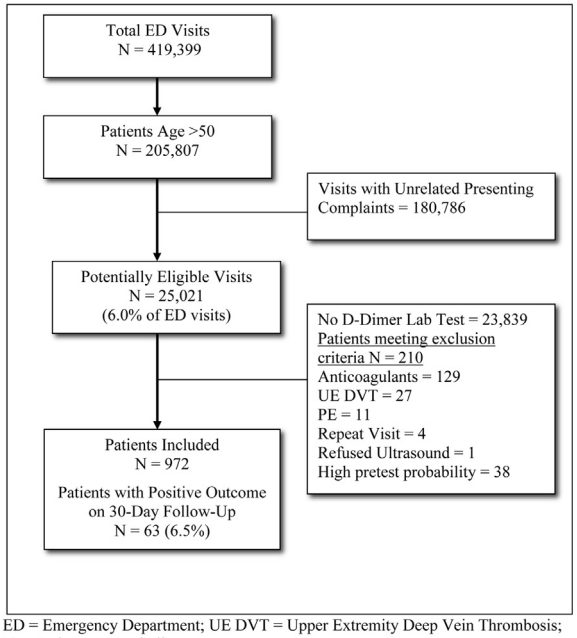
Setting

We reviewed the electronic medical records (EMRs) of patients at a tertiary care academic hospital from November 1, 2013 to January 10, 2016. The study was conducted at two EDs of The Ottawa Hospital, located in Ottawa, Ontario, Canada. Each ED sees > 80,000 visits annually.

Selection of Participants and Chart Review Method

We obtained the study list using the Ottawa Hospital Data Warehouse (OHDW), which is an electronic database that has been used previously in multiple studies (18–20). All ED visits were identified within the study period (Figure 1). Patients were excluded if they were aged < 50 years. Patients were then identified using a selected list of chief complaints from the Canadian Emergency Department Information Systems relating to lower-extremity symptoms: *bilateral leg swelling/edema*, *unilateral reddened hot limb*, *cool pulseless limb*, *lower extremity injury*, *lower extremity pain*, *joint(s) swelling*, *rash*, *localized swelling/redness*, *wound check, other skin conditions, lumps, bumps, calluses* (21). Patients were required to have a D-dimer (Innovance, Siemens AG, Munich, Germany) test ordered as part of their workup. These steps generated the list of potentially eligible ED visits.

The EMRs of these patients were then manually reviewed by two of the investigators (PR and SP), and



ED = Emergency Department; UE DVT = Upper Extremity Deep Vein Thrombosis; PE = Pulmonary Embolism

Figure 1. Study cohort and exclusions.

each patient had a standardized chart review form completed (Supplementary Appendix 1). Medical history, investigations, outcomes, and follow-up data were manually abstracted, while patient age, demographic information, and ED length of service (ED LOS) were provided by OHDW. All available documents were examined for the relevant study information, including the triage and physicians' records, imaging and laboratory results, and any consultation documents. The first 10% of the charts were reviewed by both investigators to ensure consistent data collection. Any disagreements were then reviewed by a third investigator (VT) for resolution. Patients were excluded from the study if they were pregnant, suspected of having an upper-extremity DVT or a PE, on anticoagulation therapy at a therapeutic level for > 48 h prior to presentation, or if they presented with the same symptoms within the previous 30 days. As this was a retrospective study, calculating and reporting a Wells' score for each patient was deemed unreliable. However, each chart was reviewed for the Wells' DVT criteria, as described in the original study (22). If the reviewer noted a score of 2 or more, then the patient was determined to be high risk for DVT and excluded from the study. To note, clinicians at our center routinely use pretest probability assessment scores, such as the Wells' criteria, in their assessment of suspected DVT. A patient with low pretest probability would have a D-dimer performed to help decide on imaging with duplex ultrasound, whereas a patient with high pretest probability would proceed directly to imaging as per Thrombosis Canada Guidelines (23).

Outcome Measures and Assessment

We defined a positive outcome as a confirmed DVT that required treatment. This included all above-knee DVTs, but only the below-knee DVTs that received treatment. Treatment decisions were determined locally by thrombosis consultants, who performed follow-up on all patients. A positive outcome was not assigned if the patient was anticoagulated by the emergency physician and then had treatment discontinued in follow-up. Negative D-dimers with the conventional cutoff were considered a negative outcome, as per standard of care. However, the EMR was reviewed for any repeat ED visits, diagnostic imaging, thrombosis referrals, or anticoagulation within 30 days after initial presentation to identify any missed cases of DVT.

Health System Cost Calculations

All costs are reported in Canadian dollars. We considered system-level health care costs, including emergency physician cost, imaging and interpretation cost, and anticoagulants prescribed within the hospital. Direct and indirect ED costs, as well as the cost of anticoagulants, were obtained from OHDW. Thrombosis and radiology physician billing and imaging costs were calculated using the provincial payment plan for physician services (Ontario Health Insurance Plan Schedule of Benefits). ED hospital cost was calculated by multiplying total ED LOS by unit cost of the ED per hour. ED LOS was measured from triage time to final disposition (in minutes). If a repeat ED visit for follow-up testing was warranted, the ED LOS for the two visits was added together.

The cost of the ED per hour was derived using the case costing system available at OHDW. The case costing system integrates clinical, logistical, and financial information from patient encounters at the study hospital. Physician billing is omitted from this calculation, however, any additional physician costs were considered in the overall costs and added manually as described. In 2016, the cost of the ED per hour at the study hospital was $73.41 per patient-hour.

We calculated the costs using the conventional cutoffs using our available data. The financial implications of different D-dimer cutoff values were estimated by considering the number of patients who would have decreased ED LOS and prevented additional investigations (i.e., a D-dimer between 500 ng/mL and the modified cutoff value). For these patients, we estimated the difference in their ED LOS by subtracting mean LOS in patients with a D-dimer < 500 ng/mL who did not have an ultrasound performed from the mean of patients who had a D-dimer > 500 ng/mL and went on to further investigations. The difference in their LOS served as an estimate of the additional time needed to workup a patient with a positive D-dimer. The total cost-savings of a new D-dimer cutoff was the sum of savings as a result of shortened ED LOS and savings due to prevented ultrasound imaging, anticoagulation, and thrombosis referral.

In some centers, ultrasound imaging and interpretation may be readily available, which can avoid anticoagulation and thrombosis consultation costs if the ultrasound is negative for DVT. To represent these costs, we performed a sensitivity analysis, by adding the cost savings of the added ED LOS and ultrasound imaging and interpretation, and then removing the anticoagulation and thrombosis costs.

Data Analysis

We described the diagnostic characteristics of previously established cutoffs using sensitivity and specificity with 95% CIs using the exact binomial method. We performed an ROC analysis to identify a potential novel age-adjusted rule or absolute cutoff for the study population—a cutoff that would have the best performance determined by improved specificity with a high

Table 1. Characteristics of Included Patients (n = 972)

Characteristics	Data
Female sex, n (%)	578 (59.5)
Age, y, median (IQR)	66 (58–77)
Personal history of VTE, n (%)	98 (10.1)
Active malignancy, n (%)	71 (7.3)
Bedridden or major surgery, n (%)	31 (3.2)
Estrogen use, n (%)	10 (1.0)
Paralysis, paresis, immobilization, n (%)	17 (1.8)
Personal history of coagulation disorders, n (%)	5 (0.5)
Antiplatelet use, n (%)	234 (24.1)
Positive DVT, n (%)	63 (6.5)

DVT = deep vein thrombosis; VTE = venous thromboembolism; IQR = interquartile range.

sensitivity. Sensitivity and specificity together with 95% CIs were calculated for the novel cutoff using the exact binomial method.

Sample Size

The sample size calculation was based on the primary objective of estimating the specificity of a novel D-dimer cutoff using a 95% binomial confidence interval (CI). At a specificity of 50% (the most conservative value), a sample size of 700 patients without DVT is adequate to ensure a two-sided 95% CI has a total width no greater than 0.074. Thus, our total sample size of 972 patients was more than adequate to reliably estimate the specificity.

RESULTS

Characteristics of Study Subjects

During the study period, there were 419,399 patient visits. Applying exclusion criteria, 972 patients remained (Figure 1). The clinical characteristics of the included patients are shown in Table 1. Including 30-day follow-up, 63 (6.5%) patients had confirmed DVT.

Test Performance of Cutoff Values

The sensitivity, specificity, positive predictive value, and negative predictive value (NPV) for the conventional, age-adjusted D-dimer, and the newly derived cutoff are presented in Table 2. The specificity increased for both modified approaches compared to the conventional. The age-adjusted rule increased specificity to 49.9% (95% CI 46.7–53.3%), while maintaining a high sensitivity of 100% (95% CI 94.3–100%). This is compared to the conventional cutoff with equal sensitivity and a specificity of 35.6% (95% CI 32.5–38.8%). Using the ROC curve analysis, we derived an optimal D-dimer cutoff point of 1000 ng/mL for all patients (Supplementary Appendix 2), which improved specificity to 66.3% (95% CI 63.2–69.4%) with equal sensitivity. NPV was 100% for all approaches. Overall, the use of the age-adjusted rule and the new absolute cutoff of 1000 ng/mL would have resulted in an additional 130 (13.4%) and 279 (28.7%) D-dimers below the cutoff. The number needed to test for a negative D-dimer was 2.1 and 1.6 (Table 3).

Financial Implications

We found that all age-adjusted approaches led to substantial cost savings (Table 4). The age-adjusted rule and the new cutoff of 1000 ng/mL would have resulted in 130 and 279 ED total LOS hours saved, respectively, with a total cost savings of $76,700 and $166,909. Alternatively, the ED LOS per patient was 0.15 h for the age-adjusted rule and 0.32 h for the 1000 ng/mL cutoff, which resulted in a total cost savings per patient of $79 and $172, respectively. The majority of cost savings resulted from reduced interventions, such as anticoagulation, ultrasound, and thrombosis consultation; however, there was some added benefit from reduced operational ED costs, as reflected by the ED LOS savings. If the ultrasound was performed during the index ED visit, it was very likely that the patients who were reclassified as negative per the age-adjusted D-dimer approaches would have no DVT on ultrasound. Sensitivity analysis by removing the anticoagulation and thrombosis consultation costs showed a total cost savings of $27,621 and $61,579 for the age-adjusted rule and 1000 ng/mL cutoff, respectively (Table 4).

DISCUSSION

Summary of Major Findings

This study is the first to assess the diagnostic characteristics of various D-dimer cutoffs and their cost savings in a

Table 2. Diagnostic Performance for Age-Adjusted Cutoffs

Variable	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV, % (95% CI)	PPV, % (95% CI)
Conventional cutoff value 500 ng/mL	100 (94.3–100)	35.6 (32.5–38.8)	100 (98.9–100)	9.7 (7.6–12.3)
Age-adjusted cutoff (age × 10)	100 (94.3–100)	49.9 (46.7–53.3)	100 (99.2–100)	12.2 (9.5–15.3)
Absolute cutoff value 1000 ng/mL	100 (94.3–100)	66.3 (63.2–69.4)	100 (99.4–100)	17.1 (13.4–21.3)

NPV = negative predictive value; PPV = positive predictive value; CI = confidence interval.

Table 3. Number of Patients in Whom Deep Venous Thrombosis Could Be Excluded Based on a D-Dimer Level Below the Cutoff, Stratified by Age

Variable	Age				All patients (n = 972)
	50–59 y (n = 301)	60–69 y (n = 279)	70–79 y (n = 198)	≥ 80 y (n = 194)	
Conventional cutoff value (500 ng/mL)					
No. of patients below cutoff value	150	101	53	20	324
No. of false negatives	0	0	0	0	0
No. needed to test*	2.0	2.8	3.7	9.7	3.0
Age adjusted cutoff (age × 10)					
No. of patients below cutoff value	164	138	86	66	454
No. of false negatives	0	0	0	0	0
No. needed to test*	1.8	2.0	2.3	2.9	2.1
Absolute cutoff value (1000 ng/mL)					
No. of patients below cutoff value	221	189	111	82	603
No. of false negatives	0	0	0	0	0
No. needed to test*	1.4	1.5	1.8	2.4	1.6

* Number of patients needed to obtain one D-dimer result below the cutoff value.

North American ED population. While there have been some retrospective evaluations, other studies have examined outpatient and primary care populations, and no study has examined the cost savings in a North American setting (3,12–16). We examined the performance of the age-adjusted rule in patients > 50 years compared to the conventional cutoff of 500 ng/mL. We also tested the performance of an ROC-derived cutoff of 1000 ng/mL for patients aged > 50 years. In our analysis, all cutoffs retained a high sensitivity and the NPV was 100%. Improved specificity was demonstrated for the newly derived 1000 ng/mL threshold.

Comparison to Previous Studies

The popular age-adjusted D-dimer rule has been well studied and prospectively validated in suspected PE (11). However, a similar approach has not yet been

Table 4. Financial Implications for the Conventional versus Age-Adjusted D-Dimer Cutoffs in This Cohort (n = 972)

Variable	Conventional Cutoff, 500 ng/mL (Reference)	Reduction if Age-Adjusted Cutoff, Age × 10 Applied	Reduction if Absolute Cutoff Value (1000 ng/mL) Applied
No. of patients prevented additional investigations	—	130	279
ED LOS, h			
Total	5574	144	310
Per patient	6	0.15	0.32
ED cost, C$			
Total	456,067	9763	23,253
Per patient	469	10	24
Ultrasound cost, C$			
Total	98,474	17,858	38,326
Per patient	101	18	39
Anticoagulation cost,† C$			
Total	5582	2529	5426
Per patient	6	3	6
Thrombosis consultation cost,‡ C$			
Total	100,979	46,550	99,904
Per patient	104	48	103
Total cost savings	ref	76,700	166,909
Total		79	172
Per patient			
Cost savings if all ultrasounds were performed on index visit, C$	ref	27,621	61,579
No thrombosis referral made		28	64

C$ = Canadian dollars; ED = Emergency Department; LOS = length of service.
† Ultrasound cost includes logistical cost and radiologist interpretation.
‡ Thrombosis cost includes overhead costs for clinic and physician billing.

adopted for suspected DVT. In a letter to the editor, Hamblin and colleagues described the use of this rule retrospectively in a large cohort of 6599 outpatients and found a diagnostic failure rate of only 0.05% (15). These findings are consistent with our observations and suggest that the age-adjusted D-dimer rule can safely be applied in the ED. However, a formal prospective study is required before it can be implemented in routine clinical practice. Such a study is currently underway (ClinicalTrials.gov ID: NCT02384135).

Specificity increased consistently across all age-adjusted cutoffs in our study, which translated into potential cost savings from patients being investigated less frequently and discharged from the ED earlier. The NPV was 100%, which is similar to previous studies (12,13). The greatest cost savings were noted for the derived cutoff of 1000 ng/mL. A similar approach of a cutoff of 1000 ng/mL was used in a large nonselective cohort (e.g., no age restriction, inpatients, and outpatients) with low pretest probability, resulting in reduced investigations and no missed DVT at 3 months (24). This cutoff was not independently derived with an ROC analysis, as in our study, however, it does support the safety and effectiveness of a cutoff of 1000 ng/mL in another Canadian population.

Potential Implications for Clinicians

The North American population is aging. A database study by Roberts et al. in 2008 described a 34% increase in ED visits for seniors aged 65–74 during a 10-year period (25). This trend predicted an increase in U.S. ED visits by the elderly from 6.4 million to 11.7 million over the upcoming years (26). The zero-cost intervention suggested in our study proposes a strategy to safely decrease ED LOS and associated decreased costs from unnecessary workup. Although the popular age-adjusted D-dimer rule appears to be safe for the DVT population and results in cost savings, it has not been prospectively validated and it may underperform in the DVT population when compared to an absolute cutoff of 1000 ng/mL. Applying this higher cutoff in our study population resulted in substantial cost savings, while demonstrating a similar margin of safety. This approach could be especially valuable in rural systems across North America, where access to duplex ultrasound may be limited. Broader application of an age-adjusted D-dimer strategy could increase the number of patients with a result below the diagnostic threshold, potentially preventing unnecessary anticoagulation and long travel times to obtain ultrasound imaging and thrombosis consultation.

Alternatively, it should be noted that other studies have supported a modified approach to the D-dimer based on clinical probability (27–29). The YEARS study examined the performance of a higher D-dimer threshold in patients with a low pretest probability for PE (27). For patients with a score of 0 on the YEARS algorithm (i.e., no clinical signs of DVT or hemoptysis, and PE not the most likely diagnosis), an increased D-dimer threshold of 1000 ng/mL was applied as opposed to the conventional cutoff. This approach resulted in an absolute decrease in 14% of CT pulmonary angiography in their cohort without a significant increase in false negatives. A recent multicenter assessment of the YEARS approach has demonstrated similar promising results (30). In addition to age-adjusted strategies, future studies may also apply modified D-dimer thresholds based on a pretest probability assessment.

Limitations

First, this was a single-center study, so generalizability may be limited. The outcomes data were also limited to a single center, so cases presenting to other EDs outside of the region would have been missed. Second, the study protocol selected patients with lower-extremity–related chief complaints, so patients with incorrect or inaccurate triage coding, but with suspected DVT by the physician would have been excluded. The study protocol also did not include other chief complaints, such as syncope, presyncope, chest pain, or dyspnea, which could have missed cases of concurrent PE with DVT. Third, given the retrospective nature of data collection, an accurate Wells' score could not be calculated and reported. However, as described in the Methods section, each chart was screened for the variables included in the score. Inaccurate records or omission of data may have altered the baseline characteristics and changed the pretest probability in some cases, and it is likely that we included some patients with a high pretest probability inadvertently. Although we do not know to what extent this would affect our results, likely it would have resulted in poorer performance of alternative cutoffs. Fourth, we did not distinguish between proximal or distal and acute versus chronic DVTs and have not reported proportions. Approach to anticoagulation of distal and chronic DVTs may vary depending on local practice and the treating physician (31). It is possible that our study included patients with chronic DVTs who were anticoagulated, leading to a false-positive outcome. However, from a practicing emergency physician point of view, it is important that all patients who need treatment be correctly identified during ED evaluation. Fifth, this study includes only patients aged > 50 years who had a D-dimer as part of their workup. We therefore cannot extrapolate our results to a younger population. We will also have missed a cohort of patients

that went straight to imaging without a D-dimer, though we anticipate that most of these patients would have a high pretest probability. Sixth, in our cost analysis, the thrombosis costs were a large proportion of potential cost savings. There are only a limited number of tertiary care centers with thrombosis services available and extrapolation to clinical settings with other methods of referral and follow-up may be less accurate. Finally, the observational nature of the study limits clinical use at this time. This study is hypothesis-generating only and further prospective validation is needed.

CONCLUSIONS

In a retrospective cohort of patients aged > 50 years with suspected DVT, the age-adjusted D-dimer and a cutoff of 1000 ng/mL increased the proportion of patients for whom DVT can be safely ruled out. These approaches lowered health care system costs.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jemermed.2019.01.027

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ARTICLE SUMMARY

1. Why is this topic important?

D-dimer values increase with age, thereby reducing the specificity in elderly populations being investigated for deep venous thrombosis (DVT). Age appropriate thresholds can potentially improve diagnostic accuracy and decrease unnecessary testing.

2. What does this study attempt to show?

This study evaluates the diagnostic performance and potential cost savings of previously suggested D-dimer cutoffs for emergency department (ED) patients aged > 50 years with low pretest probability of DVT. We also assessed whether a novel cutoff with improved performance could be identified.

3. What are the key findings?

In our analysis, all cutoffs retained a high sensitivity and negative predictive value was 100%. Improved specificity was demonstrated for both the age-adjusted D-dimer rule and a newly derived 1000-ng/mL threshold.

4. How is patient care impacted?

Age-modified D-dimer cutoffs could potentially result in a decrease of unnecessary investigations among older patients with corresponding decreases in ED length of stay and lower health care system costs.