Clinical patterns of presentation and attenuated inflammatory response in octo- and nonagenarians with perforated gastroduodenal ulcers

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Background. *Perforated gastrodudenal ulcer (PGDU) is an operative emergency with high mortality rates. The growing elderly population increasingly presents with need for geriatric acute operative care. Current knowledge of age-specific characteristics in presentation, diagnosis, and outcome for PGDU in the elderly is scarce.*
Methods. *We reviewed a consecutive, population-based cohort of patients with PGDU, octa- and nonagenarians were compared with younger patients for variation in patterns of presentation and outcomes. Patterns and outcomes observed included 30-day mortality, serious complications (Clavien-Dindo 3 and 4), and duration of stay.*
Results. *Of the 244 patients, 127 were women (52%); median age was 68 years; and 59 patients (24.2%) were ≥80 years. Two thirds had gastric ulcers (*n *= 168; 67.2%). On admission, hemoglobin levels, white blood cell count, and serum levels of C-reactive protein, bilirubin, and albumin differed significantly between the age groups. Diagnosis, treatment, and the occurrence of severe complications did not differ with age. The median hours of delay to definitive treatment did not differ significantly for all ages, but patients ≥80 years had a greater proportion (44.1% compared with 25.8%) of delay >12 hours (odds ratio 2.26, 95% confidence interval 1.22–4.17;* P *= .008). Overall mortality was 38 (15.6%); no deaths occurred in patients <55 years. Over one half of deaths occurred in those ≥80 years (odds ratio 4.76, 2.30–9.83;* P *< .001). Duration of hospital stay was significantly greater in elderly survivors, and fewer were discharged within a week.*
Conclusion. *Octa- and nonagenarians with PGDU present with fewer signs of peritonitis and have an attenuated inflammatory response. The very elderly have twice the risk of long delays to definitive treatment and almost 5 times increased risk of mortality. (Surgery 2016;160:341-9.)*

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One of the most frequently encountered emergency operation conditions, complicated gastroduodenal ulcer disease is a leading cause of death globally,[1] with mortality rates superseding many malignant diseases. Perforations represent the most frequent cause of mortality in gastroduodenal ulcers of all etiologies, and the incidence and mortality rates have been consistent over the past decades.[2,3] The mortality rate for perforated gastroduodenal ulcer (PGDU) is reported at between 10–30% in modern series.[2,4-9]

In PGDU, incidence and mortality increase with age in both sexes, for a 10-fold increase in incidence and a 50-fold increase in mortality in patients >60 years of age.[3] A shift in demography of PGDU is noted, with past studies having few patients (<10%) older than 60 years,[10] while current studies have a majority of patients >60 years.

Presented in part as an oral lecture at the 16th European Congress of Trauma and Emergency Surgery, May 10–12, 2015, in Amsterdam, The Netherlands.

Accepted for publication February 24, 2016.

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0039-6060/$ - see front matter

http://dx.doi.org/10.1016/j.surg.2016.02.027

Notably, the number of persons aged >60 years is increasing rapidly in both developing and developed countries.[11,12] Consequently, with the global increase in the elderly population, we can expect a proportional increase in patients in need of emergency general operations.

Emergency laparotomies are regarded as high-risk procedures with associated high mortality, particularly in the elderly.[13-15] Understanding various patterns of presentation of disease and the associated outcomes in various age groups is highly relevant. Contemporary data on specific clinical presentation, associated comorbidity, and patterns of risk that may effect outcomes in very elderly patients with PGDU are scarce. While increasing age and operative delay remain strong predictors of a poor outcome in PGDU,[5,16,17] few studies have explored potential factors related to these predictors, particularly in the very elderly.

Thus, the aim of this study was to investigate the clinical patterns of presentation and assess variation in outcomes in terms of mortality and morbidity between the younger age groups and the very elderly patients undergoing emergency operations for PGDU.

METHODS

Study design. The study represents a nonselected, consecutive, population-based patient series and is reported in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.[18]

Study ethics. The study was approved as a quality control assurance project according to the Regional Ethics Committee (REK Vest # 2011/713).

Study population. The Department of Surgery and Stavanger University Hospital (SUH), the study hospital, serves as the only hospital in the greater Stavanger area (southwestern part of Norway) and has a current catchment of about 353,000 inhabitants. All citizens of Norway are eligible for round the clock acute care services through the national health insurance coverage. Thus, our study represents a population-based, nonselective view of the patterns of the disease and subsequent care, with epidemiologic data presented previously in detail.[3] Patient data were available and identified from the unique 11-digit social security code for all Norwegian citizens, which allows for crosslink to Cause of Death Registry records in the hospital files which are updated at regular intervals in the electronic records.

All consecutive patients operated on (with either open or laparoscopic approach) for a perforated gastric or duodenal ulcer and admitted to the SUH between January 1, 2001, and December 31, 2014, were identified from the hospital administrative electronic database using ICD-10 diagnostic codes, as described previously.[17] Patient demographics, including laboratory values and clinical data, were retrieved from hospital records and operative notes. Excluded were patients with a malignant ulcer ($n = 5$), patients with PGDU identified at autopsy ($n = 3$), patients treated conservatively without operation ($n = 7$), and patients operated on suspicion of PGDU without perforation being confirmed on operation ($n = 2$).

Clinical diagnosis and operative treatment. Diagnosis was based on clinical symptoms and signs on presentation (ie, presence of peritonitis), supported by imaging as necessary, usually by abdominal computed tomography (CT). A standard, predefined set of laboratory values was obtained for all patients admitted to the emergency room with a suspected "acute abdomen."

Study aims. We sought to investigate the rate of peritonitis, sepsis, and shock for each age decade with an emphasis on the oldest age population (defined as >80 years). The primary end point was mortality defined as death within 30 days of the operation. A secondary outcome measure was the rate of complications as defined by Clavien-Dindo classes 1–5.[19] Grade 5 is death of a patient during the primary hospital stay. We defined severe (nonfatal) complications as grades 3 (requires operative, endoscopic, or radiologic intervention) and 4 (life-threatening complications).

Variables and definitions. To minimize recall bias by the patient, delay of treatment was measured as time from admittance to hospital until the start of the operation. Sepsis was defined as the presence of ≥2 of the systemic inflammatory response syndrome (SIRS) criteria (ie, temperature >38.0°C, pulse rate >90 beats per minute, respiration rate >20 per minute) in addition to infection being proved or likely.[20] Shock (as in systolic hypotension) on admission was defined as a systolic blood pressure <100 mm Hg and a heart rate >90 beats per minute; this accounts for a greater sensitivity in the elderly population.[21] Age was investigated both as a continuous and categorical variable. Categories were defined per age decade: for quartiles (<25th percentile, 25th–50th percentile, >75th percentile) and for ≥80 years of age (octagenarians and nonagenarians).

Clinical risk and comorbidity scores. The Boey score[22] was calculated based on the presence of

Table I. Patient demographics

	Age <55 y (n = *63*)	*Age ≥55 to <80 y* (n = *122*)	*Age ≥80 y* (n = *59*)	P *value*
Sex				<.001
Female	22 (35%)	63 (51.6%)	42 (71%)	
Male	41 (65%)	59 (48.4%)	17 (29%)	
Location of perforation				.503
Stomach	44 (70%)	84 (68.9%)	36 (61%)	
Duodenal	19 (30%)	38 (31.1%)	23 (39%)	
Medical history				.156
Previous ulcer history	14 (22%)	15 (12.3%)	12 (21%)	
No ulcer disease	49 (78%)	107 (87.7%)	46 (79%)	
ASA class				
ASA ≥III[23]	41 (65%)	112 (91.8%)	57 (97%)	<.001
I	1	0 (0%)	0	
II	21 (33%)	10 (8.2%)	2	
III	34 (54%)	61 (50.0%)	21 (36%)	
IV	6 (10%)	45 (36.9%)	31 (52%)	
V	1	6 (4.9%)	5 (9%)	
Boey score[22]				<.001
0	37 (59%)	26 (21.3%)	4 (7%)	
1	18 (27%)	52 (42.6%)	37 (63%)	
2	6 (10%)	35 (28.7%)	12 (20%)	
3	2	9 (7.4%)	6 (10%)	
PULP score				<.001
Median, IQR	3 (1–4)	7 (4–9)	8 (7–10)	
Charlson/Deyo				<.001
Median, IQR	1 (0–2)	4,5 (3–6)	6 (5–7)	
0–1	41 (65%)		0	
2–3	16 (25%)	34 (27.9%)	0	
4–6	5 (8%)	64 (52.5%)	40 (68%)	
≥7	1	24 (19.7%)	19 (32%)	

ASA, American Society of Anesthesiologists; *PULP*, peptic ulcer perforation; *IQR*, interquartile range.

shock, >24-hour delay from admission to operation, and degree of comorbidity. The risk score of the American Society of Anesthesiologists (ASA)[23] was based on the patients' pre-existing comorbidity with the present clinical condition at admission taken into consideration. The Peptic Ulcer Perforation score was calculated as described,[24] ranging from 0–18, with greater scores indicating greater mortality. The modified Charlson score[25] (also called Charlson-Deyo score) was reported as a continuous variable as well as in groups.

Statistical analyses. Statistical analyses were performed using statistical software for Mac (SPSS for Mac version 22; IBM Corp, Armonk, NY). For nonparametric distributions, the Kruskal-Wallis analysis of variance was used to evaluate the statistical difference for continuous values between the 3 age groups; for categorical data the χ^2 or when appropriate the Fisher exact test was used, and risk presented as an odds ratio (OR) with 95% confidence intervals (CI) where appropriate. Correlation was done with the Spearman rho, assuming a nonparametric distribution. All tests were 2-tailed.

RESULTS

During the study period, 244 patients (127 women; 52%) were included with a median age of 68 years (interquartile range 54–79 years). Gastric and not duodenal ulcers predominated in over two thirds of the patients ($n = 168$; 67.2%). Patients were categorized into 3 age groups, with the youngest and oldest patients representing roughly the lower and upper quartiles, respectively. Clinical characteristics and differences among the 3 age groups are presented in Table I.

The number of patients on ulcerogenic drugs, such as acetylsalicylic acid (ASA/aspirin) and nonsteroidal anti-inflammatory drugs (NSAIDs), increased with age, with 19 (30.2%), 57 (46.7%), and 32 (54.2%) for each age group ($P = .021$), respectively. This difference was attributed mainly to a greater use of ASA drugs (4.9%, 24.8%, and 36.8%; $P < .001$); interestingly, the use of NSAIDs

Table II. Clinical presentation and laboratory values on admission

	Age <55 y (n = *63*)	*Age ≥55 to <80 y* (n = *122*)	*Age ≥80 y* (n = *59*)	P *value*
Peritonitis, *n* (%)				.041
Present	52 (83%)	80 (65.6%)	38 (65.5%)	
Sepsis, *n* (%)				.707
Present	28 (44%)	59 (50.0%)	26 (44.8%)	
Shock, *n* (%)				.142
Present	7 (11%)	28 (23.1%)	12 (20.7%)	
Hemoglobin (g/dL)				.021
Median, IQR	14.3 (12.6–15.3)	13.9 (11.7–15.1)	12.5 (11.2–14.5)	
WBC (x 103)				.003
Median, IQR	15.7 (9.9–20.1)	12.1 (8.5–16.3)	10.4 (7.3–17.0)	
CRP (mg/L)				.001
Median, IQR	10 (2–31)	25 (9–94)	29 (10–106)	
Creatinine (μmol/L)				.056
Median, IQR	75 (68–94)	83 (66.5–114)	94 (68–134)	
Albumin (g/L)				<.001
Median, IQR	41 (38–43)	37 (33–41)	35 (29–38)	
Bilirubin (μmol/L)				.002
Median, IQR	8 (6–13)	12 (8–16)	12 (9–17)	

IQR, Interquartile range; *WBC*, white blood cell count; *CRP*, C-reactive protein.

was similar between groups (30.5%, 32.2%, and 26.3%; $P = .729$). The use of steroids was also similar among age groups (4.9%, 10.1%, and 3.5%, respectively; $P = .209$).

Smoking status was missing in 44 patients (18%), but available data there was a significant decrease in the incidence of current smokers by age, with 44 (82.4%) of those <55 years, 72 (69.2%) of those 55–80 years, and only 8 (17.8%) of those ≥80 years ($P < .001$). A past history of cancer increased with age (3.2%, 22.1%, and 13.6%; $P = .003$) as did the presence of an active diagnosis of cancer (1.6%, 16.4%, 8.5%; $P = .007$).

Clinical presentation and management. The clinical presentation differed between age groups, with a significant decline in the proportion of patients presenting with a clinical diagnosis of "peritonitis" for each age decade (Table II). Notably, this observation did not come with an associated difference in proportion of patients with sepsis or shock on admission. Presence of shock or sepsis on admission was not statistically significant among age groups (Fig, *A–C*).

On admission, hemoglobin levels, white blood cell count (WBC), and serum levels of C-reactive protein (CRP), and albumin differed significantly between the age groups as did bilirubin. Notably, serum creatinine levels were not different between age groups. Inverse correlations were found between age and WBC count (rho −0.25; $P < .001$) and also between age and albumin (rho −0.43; $P > .001$), and a positive correlation between age and CRP levels (rho 0.22; $P < .001$) was found. The immune response differed between survivors and nonsurvivors. Two thirds of all patients had the diagnosis confirmed by CT, and since 2009, all patients had a CT before an operation.

The median of hours of delay to operation did not differ between the age groups (Table III), but those aged ≥80 years had a greater proportion (44.1% compared with 25.8% for those <80 years; Fig, *A*) of delay >12 hours from admission to the operation (OR 2.26, 95% CI 1.22–4.17; $P = .008$). Patients taking steroids ($n = 17$) had a greater risk of both >12 hours delay (no steroids 27.5% versus with steroids 56.3%; OR 3.4, 95% CI 1.2–9.5; $P = .015$) and for >24 hours delay to the operation (no steroids 11.9% versus with steroids 37.5%; OR 4.4, 96% CI 1.5–13.2; $P = .004$). Taking steroids was not associated with lack of peritonitis.

Smokers had a lesser risk of being delayed for >12 hours to the operation than nonsmokers (24.8% vs 41.6%; OR 0.46, 95% CI 0.25–0.87; $P = .013$) and a difference for a delay >24 hours (9.9% and 19.5% for smokers and nonsmokers; $P = .056$), but the majority of smokers were young (<55 years). Presence of any cardiovascular disease, lung disease, active cancer, or any particular drugs was not associated with an increased risk of delay to the operation.

All patients underwent primary suture repair with an omental patch, done with either the open or laparoscopic approach. Of 28 patients (11.5%)

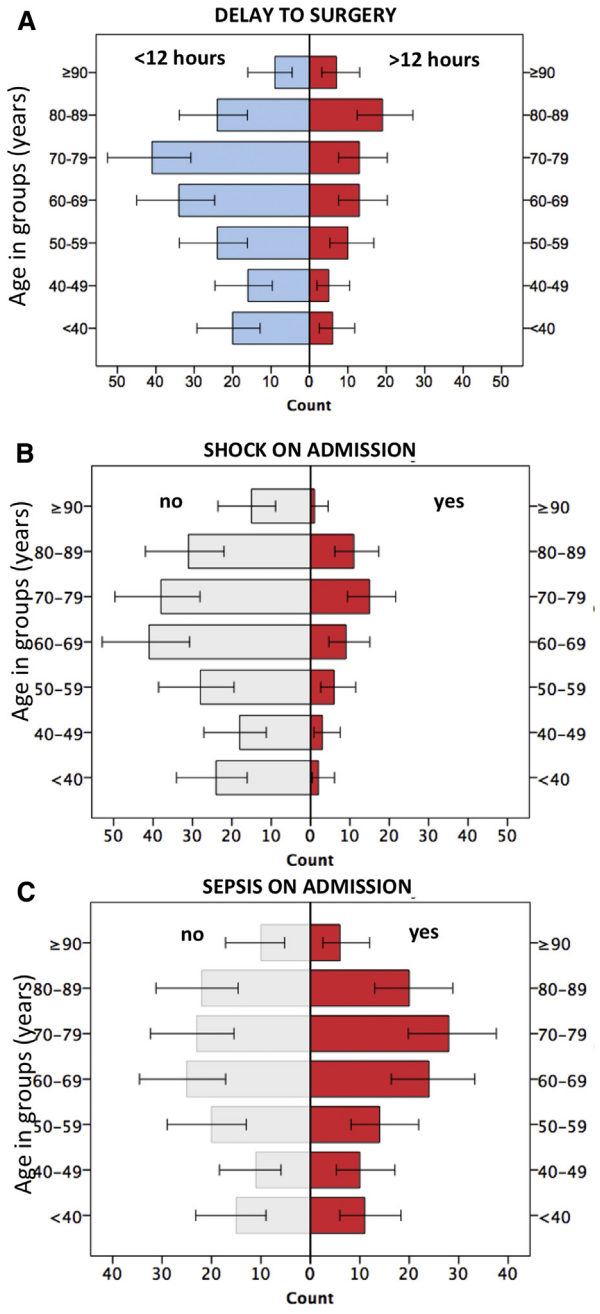

Figure. Distribution of delay to operation, presence of sepsis and shock between age groups. (*A*) Delay to operation categorized as < or ≥12 hours from admission. (*B*) Frequency of patients presenting with shock on admission. (*C*) Frequency of patients with sepsis on admission.

who had a conversion from laparoscopy to open repair, slightly more patients were ≥80 years (16.9% in octo- and nonagenarians versus 9.7% for those <80 years), but the difference was nonsignificant.

Outcomes after an operation for perforated ulcer. *Duration of stay.* As depicted in Table IV, neither overall duration of hospital stay nor time to death differed between the age groups. Notably, patients who survived accumulated a total of 3,119 hospital days, for a mean of 15.4 days per survivor. The nonagenarians accumulated 543 days (17% of all accumulated duration of hospital stay days) for survivors, for an average duration of hospital stay of 14.3 days per survivor in this age group. While almost two thirds of the youngest patients could be discharged within a week after the operation, only one third of the nonagenarians were discharged within a week.

Morbidity and mortality. The occurrence of severe complications did not differ between the age groups (Table IV), and severe complications occurred in 1 in 4 patients across all ages. Despite no difference in severe complications, a significant difference in number of deaths occurred; 38 patients (15.6%) died, with no deaths observed for the entire study period in patients <55 years, with 18 (9.7%) for patients <80 years. In contrast, in octa- and nonagenarians, 1 in 3 died within 30 days (OR 4.76, 2.30–9.83; $P < .001$).

DISCUSSION

In the current study, we found significant differences in clinical patterns of presentation and outcomes between octa- and nonagenarians compared with younger patients with PGDU. In particular, the presentation of clinically overt peritonitis decreased with age, although rates of sepsis and septic shock remained similar between age groups. Use of diagnostic imaging and types of operation were similar between age groups. Overall, no difference in duration of stay was found between age groups, but for survivors, the time to discharge was greater in octogenarians, and fewer were discharged within a week after the operation compared with the younger patients. Mortality increased with age, for an almost 5-fold increase in octa- and nonagenarians compared with younger patients. The findings are in line with other reports on outcomes in the elderly.[26-28]

The epidemiology and demographic presentation of PGDU has changed remarkably over the years. Some 3 decades ago, the number of patients ≥60 years made up only 8% of all patients, and most perforations were located in the duodenum.[10] In the current cohort, two thirds of the patients were ≥60 years, with a quarter being >80 years of age, and the majority had gastric perforations. The distributions of age, sex, and location of the ulcer compares with other current series form the Western hemisphere.[5,6,29]

Table III. Operative management

	Age groups (y)			
	<55 y (n = *63*)	*≥55 to <80 y* (n = *122*)	*≥80 y* (n = *59*)	P *value*
Delay to operation (h)				
Median (IQR)	6.3 (4.1–10.6)	5.8 (3.8–13.3)	8.0 (4.5–20.0)	.344
Delay >12 h, *n* (%)	15 (24%)	32 (26.9%)	26 (44%)	.027
Operative approach, *n* (%)				.666
Open repair	30 (48%)	58 (47.5%)	27 (46%)	
Laparoscopy	27 (43%)	52 (42.6%)	22 (37%)	
Converted (lap to open)	6 (10%)	12 (9.8%)	10 (17%)	
Duration of operation (min*)				.689
Median, IQR	90 (64–115)	81 (64–110)	91 (70–111)	

*Rounded to the nearest minute.
IQR, Interquartile range.

Table IV. Outcomes according to age groups

	Age <55 y (n = *63*)	*Age ≥55 to <80 y* (n = *122*)	*Age ≥80 y* (n = *59*)	P value
Mortality				<.001
(30 d)	0	18 (14.8%)	20 (34%)	
Morbidity				.908
Severe complications*	14 (22%)	30 (24.6%)	15 (25%)	
Overall LoS, (d)				.433
Median (IQR)	6 (5–11)	7 (5–19)	8 (5–17)	
Time to discharge,† (d)				.015
Median, IQR	6 (5–11)	7.5 (5–19)	9.5 (6–18.7)	
Discharge ≤7 d, (*n*, %)	40 (64%)	51 (50%)	13 (34%)	
Time to death, (d)				.962
Median (IQR)	(N/A)	4 (1–18.5)	3.5 (1–15.5)	

*Defined as Clavien-Dindo score 3 or 4.
†For survivors only (excluding deaths).
LoS, Length of stay; *IQR*, interquartile range; *N/A*, not applicable, as no deaths occurred in this age group.

Notably, series from developing countries still report a median age around 40 years, male predominance, and duodenal location.[30,31] Young patients may be discharged quickly in an "enhanced recovery"-like manner after an operation,[30] but this approach may not be valid in cohorts of elderly patients, where the comorbidity burden is high and recovery slower.

We believe the role of a demographic shift has important and highly relevant clinical implications for comparison of data. We have shown previously that the incidence and mortality of PGDU increase sharply with age in both sexes.[3] Because women tend to outlive men, the absolute numbers of women tends to increase with age, but mortality is similar between sexes when adjusted for the population at risk.[3]

The findings beg the question what can be done to improve results in the elderly with PGDU. Operative treatment was similar for both age groups, and we have moved increasingly toward a laparoscopic repair in recent years; we avoid resectional procedures in these frail, ill patients and prefer a primary suture repair with omentoplasty and a peritoneal wash-out. No data exists to support the superiority of either operative procedure on mortality in PGDU.[32]

A Danish quality initiative to enhance adherence to sepsis protocols in PGDU demonstrated increased compliance to several items, yet failed to demonstrate any effect on survival.[33] We have emphasized early fluid resuscitation, early initiation of broad-spectrum antibiotics, early diagnosis with use of appropriate CT imagings, and a timely operative intervention in our department policy,[34] yet we have failed to see a change in mortality over the past 15 years in the elderly, despite having zero mortality in any patient <55 years.

Compared with the younger patients, the most striking findings are the lack of overt peritonitis

and an attenuated immune response with increasing age.[35] This clinitcal presentation comes with an increased risk of long delays and a much greater mortality rate. We have shown that the less obvious clinical picture to be associated with a delay in diagnosis, a delay in treatment, and a less favorable outcome. We have no granular data to perform a further, refined, cause-effect analysis of this association but have no data to suggest that the need for prolonged resuscitation periods, problems in obtaining consent for procedures, or discussions with next of kin were associated with this delay.

Because there is no emergency physician specialty in Norway, all patients are seen immediately by on-call surgeons in the emergency department. Some patients may have been worked up or screened initially by other professionals in the emergency department, eg, internal medicine for patients admitted with "suspected chest pain" rather than "abdominal pain," for which the patient is first handed over after a nonoperative incident has been ruled out, but we have no data to investigate this more firmly. Further, this would not explain the very long delays (>12 hours) seen more often with higher age. Thus, we suspect that fewer clinical overt signs and a less prominent inflammatory response have led clinicians to a period of observation before initiation of, eg, CT or further workup. Clinical vigilance and suspicion need to be maintained in all patients of increased age.

Prediction of outcome in PGDU is complex and difficult, mirrored by the number of available proposed outcome scores.[17,24,36] The current study highlights possible clinically relevant points that should be considered. First, a relevant and clinically important absence in the presentation of peritonitis occurred in the elderly. The lack of overt signs of peritonitis in some elderly patients was not matched by a similar decrease in sepsis and patients with hypotension. Also, the octogenarians had a less prominent WBC response, despite greater CRP levels on admission. One explanation for this finding may be that the elderly patients have an attenuated immune response, because an impaired immune function may occur with increasing age.[37] Evidence for an attenuated immune response in the elderly is substantiated by the inverse relation of WBC and age in the current study, but increasing CRP levels with age were demonstrated, suggesting an intact acute phase response even in the elderly.[38] An increase in CRP was not apparent in those who eventually died, which may further point to an attenuated inflammatory response associated with poor outcome but the attenuated immune response may be just one of a series of complex end results that come with aging that reflect increased frailty in the elderly.[39]

Peritonitis was not masked because of use of steroids in this series, but the number of steroid users in our study was too small to infer any role on clinical presentation. An attenuated immune response is known to occur with increasing age and is also related to differences in the sex of the patient,[40] as noted with a shift toward females with increasing age in our study. Consequently, the elderly are at risk of both misdiagnosis and delay in treatment. Similar clinical findings of a less impressive physical examination and delayed diagnosis have been noted by others in the past,[35] although in general, emergency admissions and not specifically for PGDU.

The current study highlights the need to better understand how aging affects outcomes in emergency operations.[39] "Failure-to-rescue" has been reported to occur more frequently among elderly patients and is associated with increased mortality.[41] We do not believe that failure-to-rescue was a major cause of increased mortality in this cohort. Among patients who experienced severe complications, only 1 patient in each age group died (≥80 vs <80 years). Also, most deaths occurred soon after the operation, which may indicate a potential nonreversible condition rather than long-term effects of complications.

Our study has some strengths and weaknesses. The retrospective design over a fairly long accrual period may introduce bias in diagnostic workup and treatment, however, in the past, we have documented an increasingly uniform approach to patients with PGDU, with focus on early imaging with CT for diagnosis and a laparoscopic repair when deemed feasible.[9,34]

Further, the main pool of senior surgeons caring for the patients was consistent over the study period. Thus, no systematic bias in use of imaging or operative approach should be present. Also, we have no referrals to or from the hospital, so the cohort reflects an unselected population at risk. Notably, the definition of sepsis or septic shock is controversial in the elderly with several variations used across studies.[42] Applying strict SIRS criteria may underscore the actual rate of severe sepsis.[43]

In the elderly, hypoperfusion and "shock" may occur greater systolic blood pressures than the <90 mm Hg definition,[21] and we used 100 mm Hg as a threshold. While this definition of "shock" may increase the sensitivity to define "shocked" or

"hypoperfused" elderly patients, it may deviate from the otherwise understood definition of shock. A >40 mm Hg decrease in systolic blood pressure from baseline has also been used as a shock/hypoperfusion definition previously, which may be more appropriate for elders with hypertension.[42,44]

In conclusion, very elderly patients present less often with frank peritonitis and tend to have an attenuated immune response. Delays occur more frequently. Despite no difference in rates of CT imaging and types of operative treatment, mortality is considerably greatest in the elderly. Understanding of the frailty and attenuated immune response underlying the increased mortality risk in the elderly is needed. One additional finding is that gastric ulcers were more common than duodenal ulcers in all age groups.

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