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Original Article

Mortality rate and risk factors for gastrointestinal bleeding in elderly patients

Marco Vincenzo Lenti[a,*], Luca Pasina[b], Sara Cococcia[a], Laura Cortesi[b], Emanuela Miceli[a], Costanza Caccia Dominioni[a], Martina Pisati[a], Caterina Mengoli[a], Francesco Perticone[c], Alessandro Nobili[b], Antonio Di Sabatino[a], Gino Roberto Corazza[a], REPOSI Investigators

[a] First Department of Internal Medicine, San Matteo Hospital Foundation, University of Pavia, Pavia, Italy
[b] Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
[c] Department of Medical and Surgical Sciences, University Magna Grœcia of Catanzaro, Catanzaro, Italy

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ABSTRACT

Background: Gastrointestinal bleeding (GIB) is burdened by high mortality rate that increases with aging. Elderly patients may be exposed to multiple risk factors for GIB. We aimed at defining the impact of GIB in elderly patients.

Methods: Since 2008, samples of elderly patients (age ≥ 65 years) with multimorbidity admitted to 101 internal medicine wards across Italy have been prospectively enrolled and followed-up (REPOSI registry). Diagnoses of GIB, length of stay (LOS), mortality rate, and possible risk factors, including drugs, index of comorbidity (Cumulative Illness Rating Scale [CIRS]), polypharmacy, and chronic diseases were assessed. Adjusted multivariate logistic regression models were computed.

Results: 3872 patients were included (mean age 79 ± 7.5 years, F:M ratio 1.1:1). GIB was reported in 120 patients (mean age 79.6 ± 7.3 years, F:M 0.9:1), with a crude prevalence of 3.1%. Upper GIB occurred in 72 patients (mean age 79.3 ± 7.6 years, F:M 0.8:1), lower GIB in 51 patients (mean age 79.4 ± 7.1 years, F:M 0.9:1), and both upper/lower GIB in 3 patients. Hemorrhagic gastritis/duodenitis and colonic diverticular disease were the most common causes. The LOS of patients with GIB was 11.7 ± 8.1 days, with a 3.3% in-hospital and a 9.4% 3-month mortality rates. Liver cirrhosis (OR 5.64; CI 2.51–12.65), non-ASA antiplatelet agents (OR 2.70; CI 1.23–5.90), and CIRS index of comorbidity > 3 (OR 2.41; CI 1.16–4.98) were associated with GIB ($p < 0.05$).

Conclusions: A high index of comorbidity is associated with high odds of GIB in elderly patients. The use of non-ASA antiplatelet agents should be discussed in patients with multimorbidity.

1. Introduction

Gastrointestinal bleeding (GIB) is among the top ten reasons of gastroenterology referrals [1]. Roughly 250,000 patients are admitted to hospital for upper GIB in the US, with 20,000 deaths per year [2], whereas lower GIB yields an annual incidence rate as high as 20/100000 and represents a relevant cause of hospitalization [3–4]. GIB represents a major clinical challenge in elderly patients and despite the improvement of medical, endoscopic, and surgical treatments, still is burdened by high mortality and disability rates that increase with increasing age [5–7]. The clinical picture of elderly patients with GIB is usually characterized by paucity of symptoms, unspecific complaints, and iron deficiency anemia due to chronic blood loss, and thus may differ from that of younger individuals [7,8]. Additionally, some risk factors for GIB are more common in elderly patients, in particular the use of antiplatelet agents, which are commonly prescribed for the prevention of cardiovascular disease in up to 66% of people aged 75 and over [5,9,10]. Other relevant risk factors in the elderly include the use of anticoagulants (heparin, warfarin, and direct oral anticoagulants [DOACs]), nonsteroidal anti-inflammatory drugs (NSAIDs), selective

Abbreviations: ASA, acetylsalicylic acid; BMI, body mass index; CIRS, Cumulative Illness Rating Scale; COPD, chronic obstructive pulmonary disease; DOAC, direct oral anticoagulant; GIB, gastrointestinal bleeding; ICD, International Classification of Diseases; LOS, length of stay; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; SBT, Short Blessed Test; SIMI, Italian Society of Internal Medicine; SSRI, selective serotonin reuptake inhibitor.

* Corresponding author at: Fondazione IRCCS Policlinico San Matteo, University of Pavia, Medicina Generale I, Piazzale Golgi 19, Pavia 27100, Italy.
E-mail address: marco.lenti@unipv.it (M.V. Lenti).

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serotonin reuptake inhibitors (SSRIs), personal history of peptic ulcer disease, and colonic diverticular disease [4,7,11–15]. Multimorbidity, that is the co-occurrence of at least two diseases within a person [16], increases with aging and could be associated with an increased risk of GIB [7,8], but no clear evidence has ever confirmed this assumption. Moreover, chronic diseases tend to add up over time, generating multimorbidity, with consequent polypharmacy and high risk of drug interactions, making it even more difficult to predict the risk of GIB in these patients. Finally, mortality rates of GIB are higher in patients with at least an associated organ dysfunction [7].

Aim of this registry-based study was to describe the prevalence, causes, and mortality rate of GIB and to define potential risk factors in a large cohort of elderly patients consecutively admitted to 101 internal medicine wards across Italy.

2. Patients and methods

In 2008, the Italian Society of Internal Medicine (SIMI), in collaboration with the Istituto di Ricerche Farmacologiche Mario Negri IRCCS and the IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, set up a prospective, independent, registry study named REgistro POliterapie SIMI (REPOSI) with the aim of activating a network of internal medicine and geriatric wards in order to recruit, monitor, and study elderly patients with particular regard to multimorbidity and polytherapy. After the first run of data collection between January and December 2008, it continued every other year (2010, 2012, 2014, 2016) and it is still ongoing. Overall, 101 Italian internal medicine and geriatric wards were involved in the study. Internal medicine wards in Italy are often subspecialized in different medical fields, including cardiology, pneumology, hematology, gastroenterology, nephrology, and others. At least five random patients with > 65 years old admitted to the ward were consecutively enrolled during the one-week index periods, once every 3 months (for a total of 4 weeks per year). All the recruiting sites enrolled the required minimum number of patients. The only inclusion criterium is an age greater than, or equal to, 65. Participation in the research study was voluntary and all patients were asked to give informed consent before enrollment. The study was approved by all the local ethical committees of each recruiting site of the REPOSI study.

All the details of data collection have already been described elsewhere [17–20]. Briefly, the local treating physician completed a standardized web-based Case Report Form that included, among many other variables: social and demographic data, admitting diagnosis, medical therapy, disease burden according to the Cumulative Illness Rating Scale (CIRS) [21], cognitive impairment assessed with the Short Blessed Test (SBT) [22], any intercurrent clinical events during hospital stay, length of stay (LOS), and outcome (in-hospital death, discharged, discharged in nursing home, discharged in critical conditions). Patients were followed-up three months after discharge with a telephone interview in order to collect information on hospital re-admissions, mortality, new medical treatments, and adverse events.

For the purpose of this study, we excluded patients enrolled in the first run of data collection (2008), as many data were missing or incomplete. We have identified all possible diagnoses of GIB, both as the reason of admission to hospital or at discharge or as adverse clinical events, according to the ninth revision of the International Classification of Diseases (ICD-9), including esophageal varices and ulcer, gastric, duodenal, and jejunal ulcer, acute and atrophic gastritis with hemorrhage, other forms of gastritis and duodenitis with hemorrhage, unspecified hemorrhage of the gastrointestinal tract, small bowel and colonic diverticular disease/diverticulitis with hemorrhage, rectal and anal bleeding, and angiodysplasia of the gastrointestinal tract. Other causes of GIB, including tumors of the gastrointestinal tract and inflammatory bowel disease, were included only if associated with the ICD-9 iron deficiency anemia due to blood loss or acute post-hemorrhagic anemia. Causes of GIB were divided into upper (hemorrhage originating from the esophagus to the ligament of Treitz) *vs* lower (any site distal to the ligament of Treitz) [23] and as the cause of admission *vs* during hospital stay/at discharge. Due to the registry characteristics and the ICD-9, a further, more refined distinction between mid (from the ampulla of Vater to the terminal ileum) and lower (colonic only) GIB, was not possible. For example, the ICD-9 "bowel angiodysplasia" does not allow to distinguish between the small or the large bowel. The primary aim of the study was the evaluation of the LOS and mortality rate in patients with upper and lower GIB compared to the other patients enrolled in the registry. The secondary aim of the study was the analysis of possible risk factors for GIB, including drugs (acetylsalicylic acid [ASA], non-ASA antiplatelet agents, SSRIs, and proton pump inhibitors [PPIs]), sex, different age groups (65–74 *vs* 75–84 *vs* ≥ 85 years old), smoking, and alcohol consumption. Non-ASA antiplatelet agents include either ticlopidine or clopidogrel. To note, PPIs are not a risk factor for GIB *per se*, but they might have been prescribed because of an underlying condition predisposing to upper GIB. We also specifically looked at other possible variables, including the risk of GIB according to CIRS index of comorbidity (score > 3 *vs* ≤ 3), polypharmacy, presence or absence of anemia, obesity (according to the body mass index [BMI]), diabetes, chronic heart failure, essential hypertension, liver cirrhosis, chronic obstructive pulmonary disease (COPD), and advanced kidney disease (stage IV and V).

2.1. Statistical analysis

Data are reported as percentages for categorical variables and as means for quantitative variables. Patients with at least a diagnosis of GIB were compared to the whole cohort of patients in the REPOSI registry without GIB. Sociodemographic characteristics were compared using univariate analysis by means of Chi-squared tests for categorical variables, and *t*-tests tests for continuous variables. After a preliminary univariate analysis, the odds ratio (OR) for patients with GIB compared to the whole cohort of REPOSI patient was analyzed using multivariate logistic regression models adjusted for the chronic use of ASA, non-ASA antiplatelet agents, PPIs, SSRIs, NSAIDs, and age classes (75–84, > 84), smoking, alcohol abuse, BMI, CIRS index of comorbidity, diabetes, chronic heart failure, anemia, liver cirrhosis, essential hypertension, and COPD. An additional multivariate analysis including polypharmacy (both as a continuous variable and as split variable; < 5 drugs, 5–9 drugs, ≥ 10 drugs) was computed. Analyses were done using JMP Pro 13 (SAS Institute Inc. Cary. NC. USA) and Stata 13.0 (Stata Corp LP, College Station, Texas, USA). A p-value < .05 was considered as statistically significant.

3. Results

The flow-chart of the study is shown in Fig. 1. The REPOSI registry includes 4486 patients whose data have been prospectively collected over an 8-year time span (2010–2018). Of these patients, 3872 were included in the final analysis. A diagnosis of GIB was reported in 120 patients (mean age 79.6 ± 7.3, F:M ratio 0.9:1), with a crude prevalence of 3.1%. Upper GIB occurred in 72 patients (mean age 79.3 ± 7.6, F:M ratio 0.8:1), lower GIB in 51 patients (mean age 79.4 ± 7.1, F:M ratio 0.9:1), and both upper/lower GIB in 3 patients. Regarding upper GIB, in 41 patients (56.9%) this was the cause of admission to the ward, whereas in 66 patients (91.7%) this was reported also during the hospital stay or at discharge. Regarding lower GIB, in 34 patients (66.7%) this was the cause of admission to the ward, whereas in 37 patients (72.5%) this was also reported either during the hospital stay or at discharge. Socio-demographic and other relevant clinical characteristics of the whole cohort of patients are reported in Table 1, whereas relevant pharmacological history is reported in Table 2. Characteristics described in Table 1 did not differ among the different age groups. All the causes of GIB are reported in Fig. 2. According to the reported ICD-9 codes, none of the patients with GIB had a concurrent

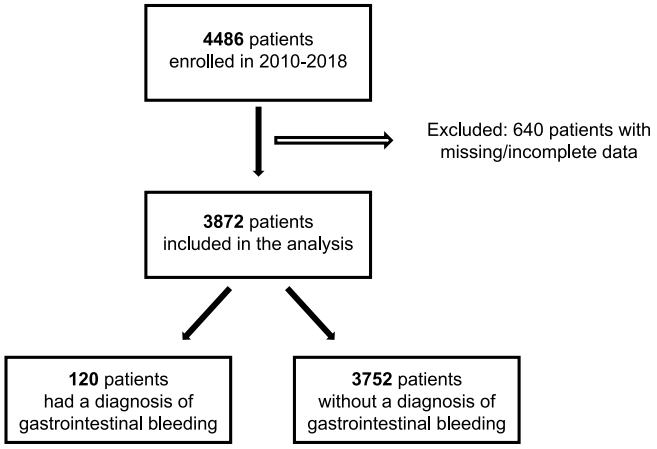

Fig. 1. Flow-chart of the study. Patients were classified as having gastrointestinal bleeding according to the ninth revision of the International Classification of Diseases (ICD-9).

Table 1
Relevant socio-demographic characteristics of patients with a diagnosis of gastrointestinal bleeding compared to the other patients enrolled in the REPOSI registry.

Variable	Gastrointestinal bleeding	REPOSI registry
Total number of patients	120	3752
Age (overall; mean ± SD)	79.6 ± 7.3	79.0 ± 7.5
65–74 (n, %)	31 (25.8)	1154 (29.8)
75–84 (n, %)	62 (51.7)	1739 (44.9)
> 84 (n, %)	27 (22.5)	979 (25.3)
Sex (F:M ratio)	0.9:1	1.1:1
BMI > 30 (n, %)	17 (15.5)	598 (15.9)
SBT normal (n, %)	45 (40.2)	1399 (37.3)
SBT moderate impairment (n, %)	25 (22.3)	599 (15.9)
SBT severe impairment (n, %)	42 (37.5)	1451 (38.7)
CIRS severity index (mean ± SD)[a]	3.4 ± 2.0	3.0 ± 1.8
Active smoking (n, %)	14 (11.8)	319 (8.5)
Current alcohol abuse (n, %)	25 (20.1)	586 (15.6)
Past alcohol abuse (n, %)	32 (26.7)	1025 (27.3)
Hospitalization within the previous year (n, %)	27 (22.5)	1200 (31.9)

Abbreviations: BMI, body mass index; CIRS, Cumulative Illness Rating Scale; SBT, Short Blessed Test; SD, standard deviation.
[a] CIRS severity index is the result of the mean of the scores attributed to all disease categories excluding psychiatric illnesses.

underlying medical condition predisposing to bleeding, including platelets disorders, thrombocytopenia, and disorder of hemostasis, and none suffered from active *H. pylori* infection. None of the patients with GIB was taking heparin or DOACs at the time of admission. The pooled LOS of patients with GIB was 11.7 ± 8.1 *vs* 11.8 ± 12.3 days of patients without GIB (p = 0.887). Fig. 3 shows the mean LOS according to the site of GIB and according to the time of diagnosis (at admission *vs* during hospital stay/at discharge). During the time of observation, regarding patients with GIB, 4/120 died in hospital (mortality rate 3.3%; 1 upper and 3 lower GIB), whereas 8/85 (excluding patients whose follow-up is not available) died within the next three months after discharge (mortality rate 9.4%; 7 upper and 1 lower GIB). On the contrary, regarding patients without GIB, after excluding patients with incomplete data, 169/3752 (4.5%) died in hospital, whereas 246/2606 (9.4%) within the next three months after discharge.

At multivariate analysis (Table 3), we found significant associations with possible risk factors for GIB, namely liver cirrhosis (OR 5.64; IC 2.51–12.65, p = 0.001), anemia (OR 2.78; IC 1.29–5.98, p = 0.008), ongoing therapy with non-ASA antiplatelet agents (OR 2.70; IC 1.23–5.90, p = 0.01), and CIRS index of comorbidity > 3 (OR 2.41; IC 1.16–4.98, p = .01). Demographic characteristics, such as sex and age, did not show any correlation with GIB. Similarly, the use of warfarin did not show any correlation with GIB, not even at univariate analysis. Finally, in order to evaluate the effect of polypharmacy on GIB, an alternative multivariate analysis including polypharmacy, after removing CIRS index of comorbidity, was computed. Polypharmacy was not associated with GIB. In particular no statistical significance was seen for all of the following: polypharmacy as a continuous variable (OR 1.03; IC 0.89–1.18, p = 0.668), use of < 5 drugs (OR 1.27; IC 0.61–2.64, p = 0.518), use of 5–9 drugs (OR 1.24; IC 0.59–2.61, p = 0.565), use of > 10 drugs (OR 1.60; IC 0.41–6.27, p = 0.498).

Table 2
Antiplatelet agents, anticoagulants, and other commonly prescribed drugs in patients with a diagnosis of gastrointestinal bleeding compared to the other patients enrolled in the REPOSI registry.

	Gastrointestinal bleeding	REPOSI registry
Antiplatelet agents and anticoagulants		
ASA (n, %)	33 (27.5)	1071 (28.5)
Non-ASA antiplatelet agents (n, %)[a]	18 (15.0)	500 (13.3)
Double antiplatelet therapy (n, %)	7 (5.8)	106 (2.9)
Vitamin K antagonists (n, %)	14 (11.7)	511 (13.6)
DOACs (n, %)	0 (0)	42 (1.1)
Other commonly prescribed drugs		
PPIs (n, %)	61 (50.8)	1815 (48.3)
High-ceiling diuretics (n, %)	38 (31.7)	1353 (36.0)
ACE inhibitors (n, %)	36 (30.0)	935 (24.9)
Beta blocking agents (n, %)	28 (23.3)	907 (24.2)
Statins (n, %)	22 (18.3)	924 (24.6)
Calcium channel blockers (n, %)	20 (16.7)	650 (17.3)
Potassium sparing diuretics (n, %)	16 (13.3)	451 (12.0)
Xantine oxidase inhibitors (n, %)	15 (12.5)	468 (12.5)
Sartans (n, %)	14 (11.7)	578 (15.4)
Thyroid hormones (n, %)	14 (11.7)	338 (9.0)
Metformin (n, %)	13 (10.8)	332 (8.8)
Benzodiazepines (n, %)	13 (10.8)	384 (10.2)
Nitrates (n, %)	8 (6.7)	441 (11.7)
SSRIs (n, %)	6 (5.0)	286 (7.6)
NSAIDs (n, %)	4 (3.3)	60 (1.6)

Abbreviations: ACE, angiotensin converting enzyme; ASA, acetylsalicylic acid; DOAC, direct oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitors.
[a] This includes ticlopidine and clopidogrel.

4. Discussion

We herein described the prevalence, causes, and the in-hospital and 3-month mortality rates of upper and lower GIB occurring in a large series of elderly patients admitted to internal medicine wards. We found that 3.1% of patients had a diagnosis of GIB, with a mortality rate that is similar to that seen in elderly patients with relevant chronic disorders, namely chronic heart failure and ischemic heart disease, COPD, chronic kidney failure, and type 2 diabetes mellitus, that were the most common diagnoses found in the REPOSI registry. To our knowledge, we also showed for the first time that a high CIRS index of comorbidity (> 3) was independently associated with GIB, regardless of polypharmacy.

The incidence of GIB increases with aging and accounts for 1% of hospital admissions in people aged 80 years and over [24,25]. Aging *per se* is a risk factor for GIB, regardless of other predisposing factors, as it has been recently demonstrated in a large prospective study on people who were not taking antiplatelet agents [26]. A prevalence of 3.1% is rather high, given that this is not a gastroenterological or surgical setting, and if we consider that most of the patients included in the registry were admitted for either cardiovascular, pulmonary, or dysmetabolic (*e.g.*, decompensated diabetes mellitus, infections or sepsis) disorders,

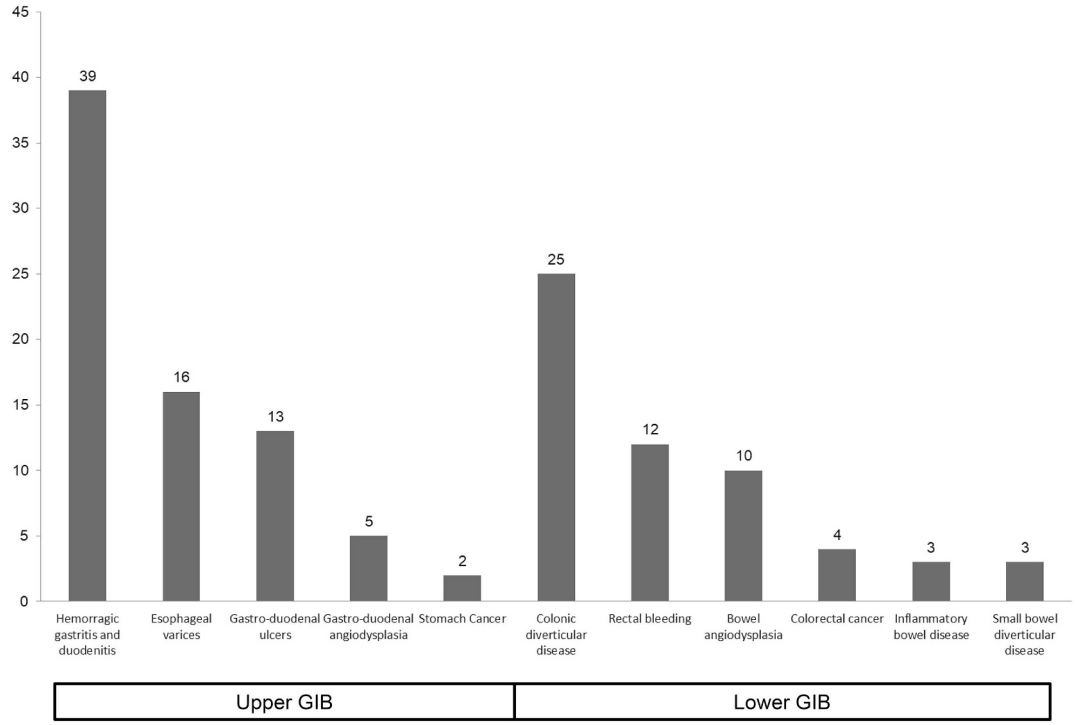

Fig. 2. Causes of gastrointestinal bleeding in the REPOSI registry. To note, in a few patients, more than one cause of GIB has been reported. Bowel angiodysplasia includes both the small bowel (without the duodenum) and the colon. Abbreviations: GIB, gastrointestinal bleeding.

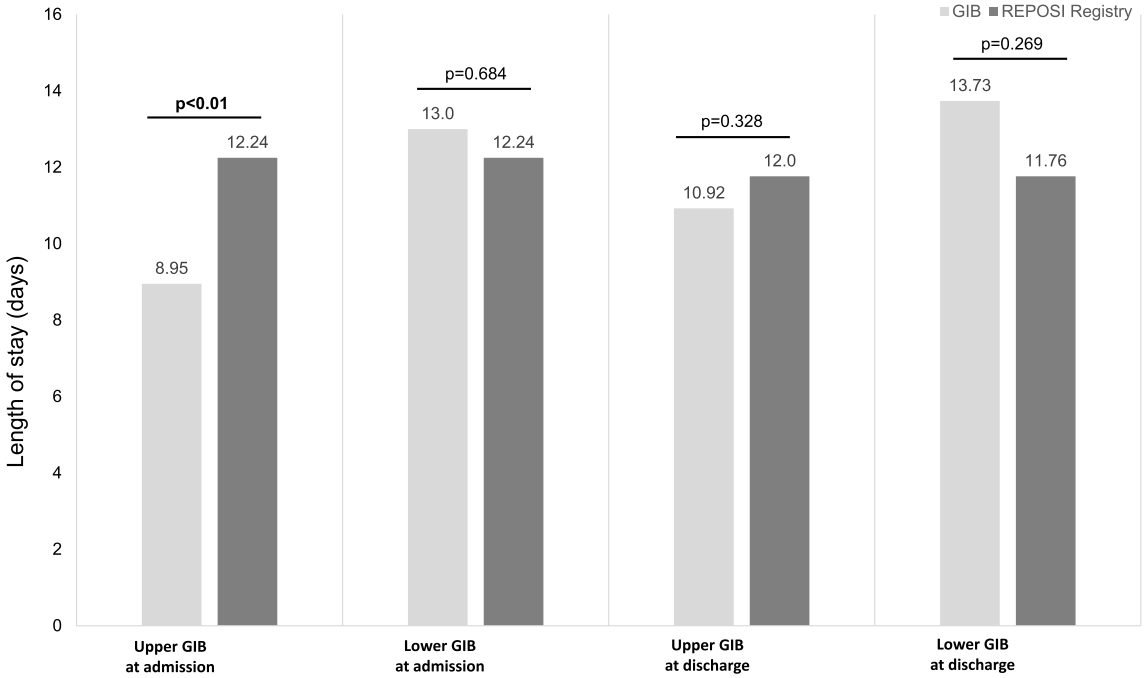

Fig. 3. Length of stay (LOS) according to the site and time of diagnosis of gastrointestinal bleeding (GIB). Notably, patients admitted with upper GIB had a significantly lower LOS compared to the other patients enrolled in the REPOSI registry. Abbreviations: GIB, gastrointestinal bleeding.

that are commonly seen in the elderly patient [27]. Furthermore, GIB was reported at the time of admission in approximately two thirds of the bleeders, thus representing an evident comorbidity in these patients. Actually, the in-hospital and 3-month mortality rates of patients with GIB (3.3% and 9.4%, respectively) did not statistically differ from those without bleeding, and this is in keeping with previous findings that reported a mortality rate of 5–10% for both upper and lower GIB [25]. Starting from these premises, our results here seem to indicate that GIB carries indeed a high risk of mortality, but what makes it particularly threatening is the co-occurrence of multiple chronic disorders, *i.e.*, multimorbidity. Actually, the overall LOS did not differ between the bleeding and the non-bleeding groups, and this corroborates the hypothesis that multimorbidity is the main responsible of this finding. However, it is worth noticing that most of the previous studies were conducted in a gastroenterological or surgical setting, that might have included different patients in terms of comorbidities and bleeding

Table 3
Multivariate analysis for possible risk factors for gastrointestinal bleeding.

Variable	Odds ratio*	95% confidence interval	p-value
ASA	0.68	0.29–1.59	0.38
Non-ASA antiplatelet agents	**2.70**	1.23–5.90	**0.01**
75–84 years old	1.49	0.66–3.30	0.32
> 84 years old	1.18	0.44–3.19	0.73
Active/previous smoking	1.70	0.63–4.58	0.28
Alcohol abuse	0.92	0.42–2.0	0.84
BMI > 30	0.60	0.20–1.76	0.35
PPIs	1.74	0.84–3.57	0.13
SSRIs	1.03	0.31–3.47	0.95
NSAIDs	1.93	0.24–15.16	0.53
CIRS index of comorbidity > 3	**2.41**	1.16–4.98	**0.01**
Anemia	**2.78**	1.29–5.98	**0.008**
Diabetes mellitus	0.37	0.08–1.60	0.18
Chronic heart failure	0.98	0.33–2.90	0.97
Liver cirrhosis	**5.64**	2.51–12.65	**0.001**
Hypertension	0.46	0.22–0.97	0.042
COPD	0.66	0.19–2.25	0.51

Abbreviations: ASA, acetylsalicylic acid; BMI, body mass index; CIRS, Cumulative Illness Rating Scale; COPD, chronic obstructive pulmonary disease; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitors.
Significant ORs and p-values are shown in bold.

* Other variables included in the analysis are as follow: sex; age < 75; years of education; previous alcohol abuse; smoking (current, former, never smoker); admission to hospital in the previous 12 months; mental impairment (according to Short Blessed Test categories); use of warfarin; use of direct oral anticoagulants; double antiplatelet agents therapy; polypharmacy; chronic renal failure (stages I-IV *vs* end stage renal disease).

severity [7].

Regarding the causes of GIB, peptic ulcer disease, including hemorrhagic gastritis, duodenitis, and gastroduodenal ulcers, was the most common cause of upper GIB (69.3%), followed by esophageal varices (21.3%). Our findings are substantially similar to those found in previous, older studies [28–30], and directly reflect the higher incidence of these conditions in the elderly. Again, colonic diverticular disease was the main cause of lower GIB (49.0%), accordingly to the high prevalence of this condition in elderly, which is estimated to be 50% among individuals older than 60 years, and even 65% over 85 years [31]. Angiodysplasia, which is usually a rare condition accounting for approximately 4–7% of obscure or upper non-variceal GIB and for an even lower percentage of lower GIB [32] was responsible for 11.4% of GIB cases in our cohort. Similarly to colonic diverticular disease, the incidence of angiodysplasia progressively increases with aging [32].

At multivariate analysis (Table 3), among the four statistically significant risk factors for GIB, liver cirrhosis showed the strongest correlation (OR 5.64). This finding is not novel, as the high risk of GIB in cirrhotic patients is well established, including both variceal and non-variceal bleeding [33,34]. The most important finding of our study is that a CIRS index of comorbidity > 3 is an independent risk factor for GIB (OR 2.41), even after adjustment for polypharmacy. Multimorbidity certainly increases with aging [35] and patients with multimorbidity may receive suboptimal treatments or incongruous prescriptions for many reasons, including a high fragmentation of care [36], due to a lack of coordination among different specialist physicians, and the lack of high-quality evidence, due to the frequent exclusion of these patients from randomized clinical trial [37]. The systematic evaluation of CIRS could be useful for stratifying patients in which additional risk factors for bleeding should be avoided or corrected, whenever possible. Finally, multimorbidity and polypharmacy are often found together, and polypharmacy could increase the risk of drug interactions and adverse effects [38,39]. However, regarding GIB, no association was found with polypharmacy, that could have represented an important confounder, thus strengthening the hypothesis that multimorbidity *per se* has a central role. Multimorbidity has a complex and multifactorial etiology, and the fine mechanisms leading to a higher risk of bleeding should be further investigated in these patients.

Interestingly, patients taking low-dose ASA did not show a higher risk of GIB (OR 0.68), while non-ASA antiplatelet agents carried an increased risk (OR 2.70). A recent, large, prospective, population-based cohort study showed that the use of low-dose ASA was associated with a higher risk of upper GIB in those who were not on PPI therapy compared to those who were [5]. In our study, almost all of the patients on ASA were also taking a PPI at the time of admission, and this could explain our findings. Moreover, a large meta-analysis of 50 randomized trials exploring any bleeding complication in patients taking antiplatelet drugs showed that the risk of GIB is very low for patients taking low-dose ASA (1.1%), whereas it is higher with thienopyridines (including ticlopidine and clopidogrel) and even quadrupled with glycoprotein IIb/IIa inhibitors [40]. The concomitant use of PPIs with clopidogrel has raised some concerns, as it is associated with a higher risk of major adverse cardiovascular events, including myocardial infarction and stroke [41]. Elderly patients treated with clopidogrel could therefore be at higher risk of GIB and cardiovascular events at the same time, thus stressing the need for discussing therapy in these patients.

Regarding anticoagulants, warfarin, when given within a normal therapeutic range, was not associated with a higher risk of GIB in our study, and this corroborates previous findings [42]. Unfortunately, the small number of patients treated with DOACs and NSAIDs (Table 2) in the REPOSI registry does not allow to draw any conclusion in this regard, and the study certainly lacks of statistical power. However, in a recently published study conducted on a large cohort of elderly patients with atrial fibrillation, reduced-dose of DOACs (rivaroxaban and dabigatran) seems to carry a lower risk of GIB compared to warfarin, with comparable efficacy [43].

We are aware of the limitations of this study. First, the REPOSI registry was not specifically set to evaluate GIB, and thus information regarding specific treatments (*e.g.*, medical, surgical, or endoscopic) is not available. Furthermore, diagnoses of GIB are only based on ICD-9 codes that do not allow a more precise characterization (*e.g.*, the distinction of causes of GIB from the small intestine only), and it is likely that only a minority of patients with severe, acute, bleeding were admitted to an internal medicine ward. The heterogeneity of the different enrolling wards may also be another limitation. Nonetheless, internal medicine wards represent a one of a kind setting where elderly patients with multimorbidity are commonly treated, and thus perfectly suit with the aim of this study. Our data should be cautiously interpreted in the light of this specific setting, that may indeed differ from others, and larger, prospective studies are needed in order to confirm our findings.

5. Conclusions

We herein characterized GIB occurring in elderly patients, showing that a high index of comorbidity, rather than the presence of a single organ failure or polypharmacy, was associated with higher odds of GIB. The use of antiplatelet agents in elderly patients should be carefully evaluated, especially in those with multimorbidity.

Conflict of interest

None to declare.

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Author contributions

All Authors participated in drafting of the manuscript or critical revision of the manuscript for important intellectual content and provided approval of the final submitted version. Individual contributions are as follows: MVL designed the study, interpreted data, and wrote the manuscript; LC and LP did and interpreted statistical analyses; SC, EM, CCD, MP, CM locally collected data and drafted a preliminary version of the manuscript; AN, FP, ADS, and GRC made the final critical revision for important intellectual contents. All Authors approved the final version of the paper.

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Appendix A. Appendix

Investigators and co-authors of the REPOSI (REgistro POliterapie SIMI, Società Italiana di Medicina Interna) Study Group are as follow:

A.1. Steering Committee

Pier Mannuccio Mannucci (Chair, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano), Alessandro Nobili (co-chair, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano), Mauro Tettamanti, Luca Pasina, Carlotta Franchi (Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano), Salvatore Corrao (ARNAS Civico, Di Cristina, Benfratelli, DiBiMIS, Università di Palermo, Palermo), Alessandra Marengoni (Spedali Civili di Brescia, Brescia), Francesco Salerno (IRCCS Policlinico San Donato Milanese, Milano), Matteo Cesari (UO Geriatria, Università degli Studi di Milano), Francesco Perticone (Presidente SIMI), Giuseppe Licata (Azienda Ospedaliera Universitaria Policlinico P. Giaccone di Palermo, Palermo, Medicina Interna e Cardioangiologia), Francesco Violi (Policlinico Umberto I, Roma, Prima Clinica Medica), Gino Roberto Corazza, (Reparto 11, IRCCS Policlinico San Matteo di Pavia, Pavia, Clinica Medica I).

Clincal data monitoring and revision: Carlotta Franchi, Laura Cortesi (Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano).

A.2. Database Management and Statistics

Mauro Tettamanti, Laura Cortesi, Ilaria Ardoino (Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano).

A.3. Investigators

A.3.1. Italian Hospitals

Domenico Prisco, Elena Silvestri, Caterina Cenci, Giacomo Emmi (Azienda Ospedaliero Universitaria Careggi Firenze, Medicina Interna Interdisciplinare); Gianni Biolo, Michela Zanetti, Martina Guadagni, Michele Zaccari (Azienda Sanitaria Universitaria Integrata di Trieste, Clinica Medica Generale e Terapia Medica); Massimo Vanoli, Giulia Grignani, Edoardo Alessandro Pulixi (Azienda Ospedaliera della Provincia di Lecco, Ospedale di Merate, Lecco, Medicina Interna); Mauro Bernardi, Silvia Li Bassi, Luca Santi, Giacomo Zaccherini (Azienda Ospedaliera Policlinico Sant'Orsola-Malpighi, Bologna, Semeiotica Medica Bernardi); Elmo Mannarino, Graziana Lupattelli, Vanessa Bianconi, Francesco Paciullo (Azienda Ospedaliera Santa Maria della Misericordia, Perugia, Medicina Interna);

Ranuccio Nuti, Roberto Valenti, Martina Ruvio, Silvia Cappelli, Alberto Palazzuoli (Azienda Ospedaliera Università Senese, Siena, Medicina Interna I); Oliviero Olivieri, Domenico Girelli, Thomas Matteazzi (Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Medicina Generale a indirizzo Immuno-Ematologico e Emocoagulativo); Mario Barbagallo, Ligia Dominguez, Floriana Cocita, Vincenza Beneduce, Lidia Plances (Azienda Ospedaliera Universitaria Policlinico Giaccone Policlinico di Palermo, Palermo, Unità Operativa di Geriatria e Lungodegenza); Marco Zoli, Ilaria Lazzari, Mattia Brunori (Azienda Ospedaliera Universitaria Policlinico S. Orsola-Malpighi, Bologna, Unità Operativa di Medicina Interna); Franco Laghi Pasini, Pier Leopoldo Capecchi, (Azienda Ospedaliera Universitaria Senese, Siena, Unità Operativa Complessa Medicina 2); Giuseppe Palasciano, Maria Ester Modeo, Carla Di Gennaro (Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Medicina Interna Ospedaliera “L. D'Agostino”, Medicina Interna Universitaria “A. Murri”); Maria Domenica Cappellini, Diletta Maira, Valeria Di Stefano, Giovanna Fabio, Sonia Seghezzi, Marta Mancarella (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Unità Operativa Medicina Interna IA); Matteo Cesari, Paolo Dionigi Rossi, Sarah Damanti, Marta Clerici, Federica Conti (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Geriatria); Gino Roberto Corazza, Emanuela Miceli, Marco Vincenzo Lenti, Martina Pisati, Costanza Caccia Dominioni (Reparto 11, IRCCS Policlinico San Matteo di Pavia, Pavia, Clinica Medica I); Giovanni Murialdo, Alessio Marra, Federico Cattaneo, Roberto Pontremoli (IRCCS Azienda Ospedaliera Universitaria San Martino-IST di Genova, Genova, Clinica di Medicina Interna 2); Maria Beatrice Secchi, Davide Ghelfi (Ospedale Bassini di Cinisello Balsamo, Milano, Divisione Medicina); Luigi Anastasio, Lucia Sofia, Maria Carbone (Ospedale Civile Jazzolino di Vibo Valentia, Vibo Valentia, Medicina interna); Francesco Cipollone, Maria Teresa Guagnano, Ermanno Angelucci, Emanuele Valeriani (Ospedale Clinicizzato SS. Annunziata, Chieti, Clinica Medica); Gerardo Mancuso, Daniela Calipari, Mosè Bartone (Ospedale Giovanni Paolo II Lamezia Terme, Catanzaro, Unità Operativa Complessa Medicina Interna); Giuseppe Delitala, Maria Berria (Azienda ospedaliera-universitaria di Sassari, Clinica Medica); Maurizio Muscaritoli, Alessio Molfino, Enrico Petrillo (Policlinico Umberto I, Sapienza Università di Roma, Medicina Interna e Nutrizione Clinica Policlinico Umberto I); Giuseppe Zuccalà, Gabriella D'Aurizio (Policlinico Universitario A. Gemelli, Roma, Roma, Unità Operativa Complessa Medicina d'Urgenza e Pronto Soccorso) Giuseppe Romanelli, Alessandra Marengoni, Alberto Zucchelli (Spedali Civili di Brescia, Brescia, Geriatria); Antonio Picardi, Umberto Vespasiani Gentilucci, Paolo Gallo, Chiara Dell'Unto (Università Campus Bio-Medico, Roma, Medicina Clinica-Epatologia); Giorgio Annoni, Maurizio Corsi, Giuseppe Bellelli, Sara Zazzetta, Paolo Mazzola, Hajnalka Szabo, Alessandra Bonfanti (Università degli studi di Milano-Bicocca Ospedale S. Gerardo, Monza, Unità Operativa di Geriatria); Franco Arturi, Elena Succurro, Mariangela Rubino (Università degli Studi Magna Grecia, Policlinico Mater Domini, Catanzaro, Unità Operativa Complessa di Medicina Interna); Maria Grazia Serra, Maria Antonietta Bleve (Azienda Ospedaliera “Cardinale Panico” Tricase, Lecce, Unità Operativa Complessa Medicina); Laura Gasbarrone, Maria Rosaria Sajeva (Azienda Ospedaliera Ospedale San Camillo Forlanini, Roma, Medicina Interna 1); Antonio Brucato, Silvia Ghidoni (Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Medicina 1); Fabrizio Fabris, Irene Bertozzi, Giulia Bogoni, Maria Victoria Rabuini, Elisabetta Cosi (Azienda Ospedaliera Università di Padova, Padova, Clinica Medica I); Roberto Manfredini, Fabio Fabbian, Benedetta Boari, Alfredo De Giorgi, Ruana Tiseo (Azienda Ospedaliera - Universitaria Sant'Anna, Ferrara, Unità Operativa Clinica Medica); Giuseppe Paolisso, Maria Rosaria Rizzo, (Azienda Ospedaliera Universitaria della Seconda Università degli Studi di Napoli, Napoli, VI Divisione di Medicina Interna e Malattie Nutrizionali dell'Invecchiamento); Claudio Borghi, Enrico Strocchi, Valeria De Sando, Ilenia Pareo (Azienda Ospedaliera Universitaria Policlinico S.

Orsola-Malpighi, Bologna, Unità Operativa di Medicina Interna Borghi); Carlo Sabbà, Francesco Saverio Vella, Patrizia Suppressa, Pasquale Agosti, Andrea Schilardi, Francesca Loparco (Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Medicina Interna Universitaria C. Frugoni); Luigi Fenoglio, Christian Bracco, Alessia Valentina Giraudo (Azienda Sanitaria Ospedaliera Santa Croce e Carle di Cuneo, Cuneo, S. C. Medicina Interna); Silvia Fargion, Giulia Periti, Marianna Porzio, Slivia Tiraboschi (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Medicina Interna 1B); Flora Peyvandi, Raffaella Rossio, Barbara Ferrari, Giulia Colombo (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Medicina Interna 2); Valter Monzani, Valeria Savojardo, Christian Folli, Giuliana Ceriani (Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Medicina Interna Alta Intensità); Francesco Salerno, Giada Pallini (IRCCS Policlinico San Donato e Università di Milano, San Donato Milanese, Medicina Interna); Franco Dallegri, Luciano Ottonello, Luca Liberale, Lara Caserza, Kassem Salam (Università di Genova, Genova, Medicina Interna 1); Nicola Lucio Liberato, Tiziana Tognin (ASST di Pavia, UOSD Medicina Interna, Ospedale di Casorate Primo, Pavia); Giovanni Battista Bianchi, Sabrina Giaquinto (Ospedale “SS Gerosa e Capitanio” di Lovere, Bergamo, Unità Operativa Complessa di Medicina Generale, Azienda Ospedaliera “Bolognini” di Seriate, Bergamo); Francesco Purrello, Antonino Di Pino, Salvatore Piro (Ospedale Garibaldi Nesima, Catania, Unità Operativa Complessa di Medicina Interna); Renzo Rozzini, Lina Falanga, Elena Spazzini, Camillo Ferrandina (Ospedale Poliambulanza, Brescia, Medicina Interna e Geriatria); Giuseppe Montrucchio, Paolo Petitti (Dipartimento di Scienze Mediche, Università di Torino, Città della Scienza e della Salute, Torino, Medicina Interna 2 U. Indirizzo d'Urgenza); Raffaella Salmi, Piergiorgio Gaudenzi (Azienda Ospedaliera-Universitaria S. Anna, Ferrara, Unità Operativa di Medicina Ospedaliera II); Francesco Violi, Ludovica Perri (Policlinico Umberto I, Roma, Prima Clinica Medica); Raffaele Landolfi, Massimo Montalto, Antonio Mirijello (Policlinico Universitario A. Gemelli, Roma, Clinica Medica); Luigina Guasti, Luana Castiglioni, Andrea Maresca, Alessandro Squizzato, Marta Molaro, Alessandra Grossi (Università degli Studi dell'Insubria, Ospedale di Circolo e Fondazione Macchi, Varese, Medicina Interna I); Marco Bertolotti, Chiara Mussi, Maria Vittoria Libbra, Giulia Dondi, Elisa Pellegrini, Lucia Carulli (Università di Modena e Reggio Emilia, AUSL di Modena, Modena, Nuovo Ospedale Civile, Unità Operativa di Geriatria e U·O. di Medicina a indirizzo Metabolico Nutrizionistico); Francesco Perticone, Lidia Colangelo, Tania Falbo (Università Magna Grecia Policlinico Mater Domini, Catanzaro, Unità Operativa Malattie Cardiovascolari Geriatriche); Vincenzo Stanghellini, Roberto De Giorgio, Eugenio Ruggeri, Sara del Vecchio (Dipartimento di Scienze Mediche e Chirurgiche, Unità Operativa di Medicina Interna, Università degli Studi di Bologna/Azienda Ospedaliero-Universitaria S.Orsola-Malpighi, Bologna); Andrea Salvi, Roberto Leonardi, Giampaolo Damiani (Spedali Civili di Brescia, U.O. 3a Medicina Generale); Armando Gabrielli, William Capeci, Massimo Mattioli, Giuseppe Pio Martino, Lorenzo Biondi, Pietro Pettinari (Clinica Medica, Azienda Ospedaliera Universitaria - Ospedali Riuniti di Ancona); Riccardo Ghio, Anna Dal Col (Azienda Ospedaliera Università San Martino, Genova, Medicina III); Salvatore Minisola, Luciano Colangelo (Policlinico Umberto I, Roma, Medicina Interna F e Malattie Metaboliche dell'osso); Antonella Afeltra, Benedetta Marigliano, Maria Elena Pipita (Policlinico Campus Biomedico Roma, Roma, Medicina Clinica); Pietro Castellino, Julien Blanco, Luca Zanoli, Samuele Pignataro (Azienda Ospedaliera Universitaria Policlinico – V. 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Giovanni Battista Molinette, Torino); Giorgio Galanti, Gabriele Mascherini, Cristian Petri, Laura Stefani (Agenzia di Medicina dello Sport, AOUC Careggi, Firenze); Margherita Girino, Valeria Piccinelli (Medicina Interna, Ospedale S. Spirito Casale Monferrato, Alessandria); Francesco Nasso, Vincenza Gioffrè, Maria Pasquale (Struttura Operativa Complessa di Medicina Interna, Ospedale Santa Maria degli Ungheresi, Reggio Calabria); Giuseppe Scattolin, Sergio Martinelli, Mauro Turrin (Medicina Interna, Ospedale di Monselice, Padova); Leonardo Sechi, Cristina Catena, Gianluca Colussi (Clinica Medica, Azienda Ospedaliera Universitaria, Udine); Nicola Passariello, Luca Rinaldi (Presidio Medico di Marcianise, Napoli, Medicina Interna); Franco Berti, Giuseppe Famularo, Tarsitani Patrizia (Azienda Ospedaliera San Camillo Forlanini, Roma, Medicina Interna II); Roberto Castello, Michela Pasino (Ospedale Civile Maggiore Borgo Trento, Verona, Medicina Generale e Sezione di Decisione Clinica); Gian Paolo Ceda, Marcello Giuseppe Maggio, Simonetta Morganti, Andrea Artoni(Azienda Ospedaliero Universitaria di Parma, U.O·C Clinica Geriatrica); Stefano Del Giacco, Davide Firinu, Francesca Losa, Giovanni Paoletti (Policlinico Universitario Dulio Casula, Azienda Ospedaliero-Universitaria di Cagliari, Cagliari, Medicina Interna, Allergologia ed. Immunologia Clinica); Giuseppe Montalto, Anna Licata, Valentina Malerba (Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone, Palermo, U.O·S Prevenzione Malattie Epatobiliari); Lasco Antonino, Giorgio Basile, Catalano Antonino (Azienda Ospedaliera Universitaria Policlinico G. Martino, Messina, Unità Operativa di Geriatria); Lorenzo Malatino, Benedetta Stancanelli, Valentina Terranova, Salvatore Di Marca (Azienda Ospedaliera per l'Emergenza Cannizzaro, Catania, (Clinica Medica Università di Catania); Patrizia Mecocci, Carmelinda Ruggiero, Virginia Boccardi (Università degli Studi di Perugia-Azienda Ospedaliera S.M. della Misericordia, Perugia, Struttura Complessa di Geriatria); Tiziana Meschi, Fulvio Lauretani, Andrea Ticinesi (Azienda Ospedaliera Universitaria di Parma, U.O Medicina Interna e Lungodegenza Critica); Pietro Minuz, Luigi Fondrieschi (Azienda Ospedaliera Universitaria Verona, Policlinico GB Rossi, Verona, Medicina Generale per lo Studio ed. il Trattamento dell'Ipertensione Arteriosa); Mario Pirisi, Gian Paolo Fra, Daniele Sola (Azienda Ospedaliera Universitaria Maggiore della Carità, Medicina Interna 1); Massimo Porta, Piero Riva (Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino, Medicina Interna 1 U); Roberto Quadri (Ospedale di Ciriè, ASL TO4, Torino, S.C. Medicina Interna); Giorgio Scanzi, Caterina Mengoli, Stella Provini, Laura Ricevuti (ASST Lodi, Presidio di Codogno, Milano, Medicina); Emilio Simeone, Rosa Scurti, Fabio Tolloso (Ospedale Spirito Santo di Pescara, Geriatria); Roberto Tarquini, Alice Valoriani, Silvia Dolenti, Giulia Vannini(Ospedale San Giuseppe, Empoli, USL Toscana Centro, Firenze, Medicina Interna I); Alberto Tedeschi, Lucia Trotta (ASST Fatebenefratelli - Sacco, Milano, Medicina Interna a indirizzo Pneumologico); Riccardo Volpi, Pietro Bocchi, Alessandro Vignali (Azienda Ospedaliera Universitaria di Parma, Clinica e Terapia Medica); Sergio Harari, Chiara Lonati, Mara Cattaneo (Ospedale San Giuseppe Multimedica Spa, U.O. Medicina Generale).

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