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ORIGINAL ARTICLE

Mortality and prognostic factors in patients with bullous pemphigoid: a retrospective multicenter Italian study

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Abstract

Introduction Bullous pemphigoid is the most common autoimmune bullous dermatosis. In recent years several studies have tried to identify the main factors of the disease related with an increased risk of death. The aim of this multicenter Italian study was to assess the risk score of death considering epidemiologic, clinical, immunological, and therapeutic factors in a cohort of patients affected by bullous pemphigoid and try to identify the cumulative survival up to 120 months.

Methods We retrospectively reviewed the medical records of patients with bullous pemphigoid who were diagnosed between 2005 and 2020 in the 12 Italian centers. Data collected included sex, age at the time of diagnosis, laboratory findings, severity of disease, time at death/censoring, treatment, and multimorbidity.

Results A total of 572 patients were included in the study. The crude mortality rate was 20.6%, with an incidence mortality rate of 5.9 × 100 person/year. The mortality rate at 1, 3, 5, and 10 years was 3.2%, 18.2%, 27.4% and 51.9%, respectively. Multivariate model results showed that the risk of death was significantly higher in patients older than 78 years, in presence of multimorbidity, anti-BP180 autoantibodies >72 U/mL, or anti-BP230 > 3 U/mL at diagnosis. The variables jointly included provided an accuracy (Harrel's Index) of 77% for predicting mortality.

Conclusion This study represents the first nationwide Italian study to have retrospectively investigated the mortality rates and prognostic factors in patients with bullous pemphigoid. A novel finding emerged in our study is that a risk prediction rule based on simple risk factors (age, multimorbidity, steroid-sparing drugs, prednisone use, and disease severity) jointly considered with two biomarkers routinely measured in clinical practice (anti-BP230 and anti-BP180 autoantibodies) provided about 80% accuracy for predicting mortality in large series of patients with this disease.

[†]Equally contributed to this work.

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Conflicts of interest

The authors declare no potential conflict of interest.

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Introduction

Bullous pemphigoid (BP) is the most common autoimmune bullous dermatosis, clinically characterized by pruritic, urticarial plaques, and tense bullae. It mainly occurs in elderly patients, and the diagnosis is confirmed by the presence of subepidermal bullae on histology, the direct immunofluorescence analysis of perilesional skin and/or the serum detection by enzyme-linked immunosorbent assay (ELISA) of autoantibodies (AAbs) against BP180 (type XVII collagen) and/or BP230, and components of junctional adhesion complexes called hemidesmosomes, which promote the dermoepidermal cohesion.[1]

In recent years, several studies have tried to identify the main factors of the disease related with an increased risk of death. A late age onset of BP and multimorbidity may negatively impact the prognosis, as reported in the literature.[2,3] Patients with higher serum levels of AAbs against BP180 NC16A showed a higher 1-year mortality rate.[4] In addition, AAbs against BP230 seem to be more frequent in older patients.[4]

The introduction of oral corticosteroids has revolutionized the prognosis of this immunomediated disease.[5] Nowadays, topical and systemic corticosteroids (CS) remain the first option of treatment for patients with BP, often combined with immunomodulatory and immunosuppressant agents.[6–10] However, it is a matter of debate which dosage of oral CS is appropriate in order to control the disease and thus reduce mortality on the one hand and minimize the risk of adverse reactions on the other hand. From recent systematic reviews, it appears that starting doses of prednisolone greater than 0.75 mg/kg/day does not seem to give additional benefits and instead a lower administration dose (0.5 mg/kg/day) may be adequate for disease control in more participants than was previously believed. This would be expected to reduce the incidence and severity of adverse reactions (especially death) associated with the treatment.[11] Moreover, the reported worldwide mortality rates varied significantly, ranging from 6 to 41% in the first year following a BP diagnosis, according to the geographical area in which the study was conducted.[2,12–17]

The aim of this multicenter Italian study was to assess the risk score of death considering epidemiologic, clinical, immunological, and therapeutic factors in a cohort of patients affected by BP and, in addition, try to identify the cumulative survival up to 120 months in Italy.

Methods

We retrospectively reviewed the medical records of all patients with BP who were diagnosed between January 2005 and June 2020 in the 12 Italian centers which participated in the study.

At least two of the following three criteria had to be fulfilled to participate in the study: (1) histopathology consistent with BP (ie, subepidermal blisters with infiltration of inflammatory cells, particularly eosinophils); (2) direct immunofluorescence showing linear C3 and/or IgG along the basement membrane zone; and (3) IgG AABs against BP180 and/or BP230 antigen detected by ELISA (provided by EUROIMMUN Medizinische Labordiagnostika AG, Lubeck, Germany) or Western blot analysis.[18] Patients with predominant or exclusive mucosal disease were excluded because we intended to compare our findings with those of previous studies.[19] All patients enrolled in this study were treated with topical steroids (clobetasol propionate cream 0.05% twice daily, for a total of 30–40 g/weekly, depending on the body weight and on disease severity, until 15 days after disease control, thereafter corticosteroid tapering over several months) plus oral corticosteroids (low dosage: prednisone <0.5 mg/kg/day; moderate dosage: prednisone 0.5–0.8 mg/kg/day; high dosage: prednisone >0.8 mg/kg/day) with or without other immunosuppressant corticosteroid-sparing agents, such as azathioprine, mycophenolate mofetil, methotrexate, and dapsone. Therapy was chosen according to the disease severity of BP and comorbidities of the patients.

Data collected included sex, age at the time of diagnosis, laboratory findings, severity of disease, dosage and kind of systemic treatments, time at death, and comorbidities. Comorbidities diagnosed by primary care physicians or other specialty physicians as documented in the medical records were considered. We recorded comorbidities which were present at the time of diagnosis, and we used the term multimorbidity, already adopted in other articles,[3,20] referring to the coexistence of two or more chronic medical conditions occurring within the same individual, in distinction to the simple term comorbidity, which refers to an index disorder to which to correlate the onset of other diseases. Multimorbidity better describes what we observed in elderly patients, in whom it is often not possible to identify a dominant disease. It has also been demonstrated that the presence of multimorbidity is associated with a decreased

quality of life, reduced functional status, higher healthcare utilization, poorer outcomes, and ultimately death.[3,13,21]

BP disease severity was graded at the time of diagnosis based on the percentage of body surface area (BSA) involvement as follows: mild, <10%; moderate, 10% to 30%; and severe, >30%.[21] We checked all the active skin lesions, such as blisters and urticarial papules and plaques; we did not include healed lesions, such as post-inflammatory hyperpigmentation. Only patients who had at least 3 months of follow-up have been included in this study.

Statistical analysis

The follow-up period was calculated as the time (in months) spanning from the diagnosis date to death or the last observation. Data were summarized as median and interquartile range or absolute number and percentage. A standard Kaplan–Meier (K–M) analysis was applied to identify cumulative survival at 12, 36, and 60 months. To identify the demographic and clinical correlates of death, univariate Cox survival analysis was performed. For the multivariate model, only variables with P values ≤0.15 were selected. Because of the statistical association with the outcome of both anti-BP230 AAbs levels (median value of 3 U/mL and standard cut-off of 9 U/mL, respectively), different models were performed.

The prognostic accuracy of predictive factors was investigated by the Harrell's Concordance Index. By using the multivariate prognostic model, a risk score derived from predictive factors was calculated on individual basis. The regression coefficients of risk factors (b) were summed up,[22] then divided by this sum, and the result multiplied by 100, thus obtaining a risk prediction rule ranging from 0% to 100%. A comparison of cumulative survival curves was made, first of the observed values through the K–M estimate and the second of estimated values through the Cox model. Data were analyzed with STATA/IC 13.1 for Windows (College Station, TX) and RStudio-1.2.5033.1.

Results

A total of 572 patients were included in the study (see the flow of patients across the selection steps in Fig. 1), the median age was 78 years (IR70.0–84.3), and 53% were females. The 51.7% of patients had multimorbidity at the time of BP diagnosis (Table 1).

Anti-BP180 AAbs levels >72 U/mL show significant association with disease severity (Chi2 P 0.006) and anti-BP230 AAbs with age (Wilcoxon P 0.01) and multimorbidity (Chi2 P 0.003), although age and multimorbidity are strongly associated (Wilcoxon $P < 0.001$). Lower values of prednisone dosage (<0.5 mg/kg/day) were associated with the presence of multimorbidity (OR 1.47 95%CI 1.06–2.05, P 0.02).

The crude mortality rate was of 20.6%, with an incidence mortality rate of 5.9 × 100 persons/year. The median survival time by K–M estimate was of 120 months, until 60 months about 3/4 of patients were still alive. The mortality rate at 1, 3, 5, and 10 years was 3.2%, 18.2%, 27.4% and 51.9%, respectively (Appendix S1).

Univariate analysis

Univariate analysis (Table 2) showed that the risk of death was higher with the increase of age (as continuous and median value), anti-BP230 > 3 U/mL, in presence of multimorbidity and of steroid sparing drugs. With a statistical significance of

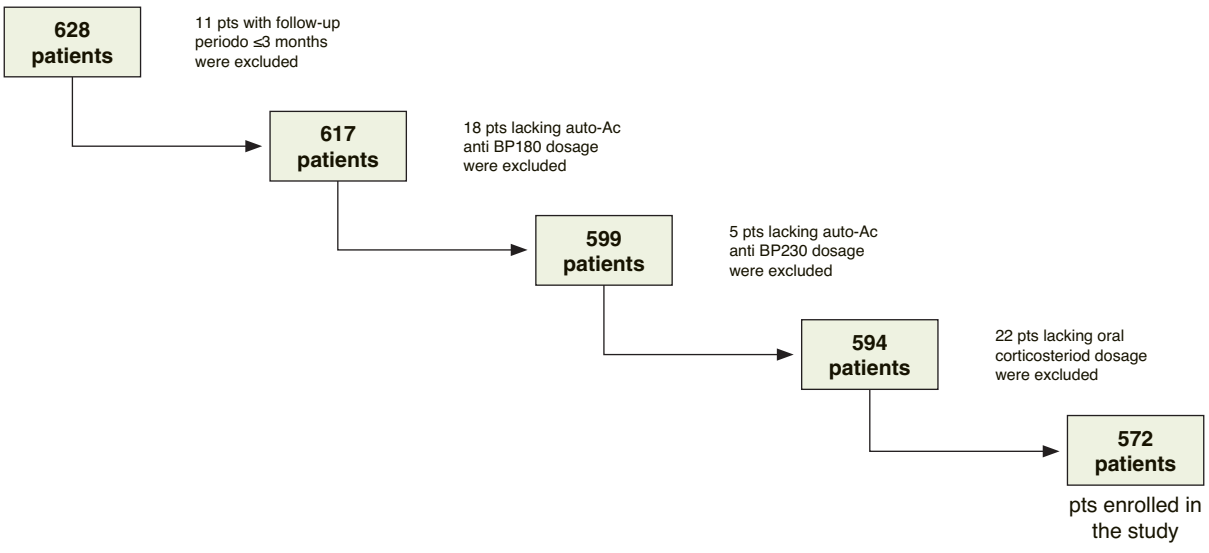

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Figure 1 Flow diagram summarizing patients included in the study.

Table 1 Baseline characteristics, overall and by outcome

		Alive	Dead	Total
Sex	Females	242 (53.3)	62 (52.5)	304 (53.1)
Age	Median (RQ)	76 (68–82.8)	85 (81–89.8)	78 (70–84.3)
Autoantibodies anti-BP180 class	≥20 U/mL	382 (84.1)	105 (89)	487 (85.1)
Autoantibodies anti-BP180 levels (U/mL)	Median (RQ)	70.8 (37–134.2)	89.5 (40–153.8)	72 (37–146.9)
Autoantibodies anti-BP230 class	≥9 U/mL	183 (40.3)	60 (50.8)	243 (42.5)
Autoantibodies anti-BP230 levels (U/mL)	Median (RQ)	3 (1–50.8)	10 (2–55.2)	3 (1–53.3)
Systemic steroids (equivalent dose to prednisone)	Median (RQ)	5 (4–5)	4 (3–5)	5 (3–5)
Equivalent dose to prednisone	Low (0.1–0.4 mg/kg/die)	207 (45.6)	64 (54.2)	271 (47.4)
	Moderate (0.5–0.8 mg/kg/die)	226 (49.8)	50 (42.4)	276 (48.3)
	High (0.9–1.2 mg/kg/die)	21 (4.6)	4 (3.4)	25 (4.4)
Steroid sparing agents	Yes	132 (29.1)	20 (16.9)	152 (26.6)
Disease severity	Severe	114 (25.1)	35 (29.7)	149 (26)
Multimorbidity	Yes	202 (44.5)	94 (79.7)	296 (51.7)

10%, lower values of prednisone dosage (<0.5 mg/kg/day) were associated with higher risk of death. Last, anti-BP180 ≥ 72 U/mL and the presence of severe disease show association with death. with a significance of 15%.

Multivariate analysis

Multivariate model results (Table 3) show that, being constant the other variables, the HR of dying was six times higher in patients older than 78 years and 2.6 times higher in patients with multimorbidity than in those of the corresponding reference categories. In the same model, the death risk resulted to be 47% higher in patients with anti-BP180 > 72 U/mL and 57% higher in people with anti-BP230 > 3 U/mL (see Appendix S2 for the model adjusted by anti-BP230 AAbs levels of 9 U/mL). Prednisone dosage, disease severity, and steroid sparing did not achieve statistical significance.

Overall, the variables jointly included into the model reported in Table 3 provided an accuracy (Harrel's Index) for predicting mortality of 77%. Similar results derived by the Cox model adjusted by anti-BP230 standard cut-off (Appendix S2).

Accordingly, the estimated survival curve by a Cox regression model including the variables listed in Table 3 adequately approached the observed survival curve as estimated by the Kaplan–Meier method, indicating that the predicted risk was consistent with the observed risk across the study period (Fig. 2).

The weight of each risk factor for predicting mortality is reported in the last column in Table 3 as well as in Fig. 3. Age > 78 years (39.1%), multimorbidity (20.8%), and no steroid-sparing drugs (10.6%) resulted to be the most important prognostic variables in rank order for mortality, followed by

Table 2 Univariate Cox survival models

	Categories	HR (95% CI)	*P*	C-index
Sex	Males vs. females	1.02 (0.71–1.47)	0.90	49.6
Age		1.13 (1.10–1.16)	<0.001	78.1
Age median	>78 vs. ≤78 years	7.62 (4.66–12.46)	<0.001	70.4
Autoantibodies anti-BP180 categ	≥20 vs. <20 U/mL	1.39 (0.78–2.47)	0.27	51.5
Autoantibodies anti-BP180 median	≥72 vs. <72 U/mL	1.31 (0.91–1.88)	0.15	55.5
Autoantibodies anti-BP180 U/mL		1.00 (1.00–1.00)	0.11	55.8
Autoantibodies anti-BP230 categ	≥9 vs. <9 U/mL	1.66 (1.15–2.38)	<0.01	57.4
Autoantibodies anti-BP230 median	>3 vs. ≤3 U/mL	1.60 (1.11–2.32)	0.01	56.6
Autoantibodies anti-BP230 U/mL		1.00 (1.00–1.00)	0.24	59.0
Prednisone mg/kg/die		0.94 (0.85–1.04)	0.21	54.4
Prednisone dosage	Moderate vs. Low	0.73 (0.51–1.06)	0.10	53.7
	High vs. Low	0.56 (0.20–1.54)	0.26	
Prednisone median	<0.5 vs. ≥0.5 mg/kg/die	1.39 (0.97–2.00)	0.07	53.7
Steroid sparing agents	No vs. yes	1.93 (1.19–3.12)	<0.01	55.6
Disease severity	Severe vs. Low-moderate	1.34 (0.90–2.00)	0.15	51.9
Multimorbidity	Yes vs. no	4.54 (2.89–7.11)	<0.001	65.4

Table 3 Multivariate Cox model

	HR (95% CI)	*P* value	Risk scores
Age > 78 vs. ≤78	6 (3.57–10.09)	<0.001	39.1
Median180 > 72 vs. ≤72 U/mL	1.47 (1.01–2.13)	0.04	8.4
Median 230 > 3 vs. ≤3 U/mL	1.57 (1.07–2.31)	0.02	9.9
Median prednisone <0.5 vs. ≥0.5 mg/kg/die*	1.3 (0.89–1.89)	0.17	5.7
Sparing no vs. yes	1.62 (0.99–2.67)	0.06	10.6
Multimorbidity yes vs. no	2.6 (1.62–4.15)	<0.001	20.8
Disease severity yes vs. no	1.29 (0.85–1.95)	0.24	5.5

Shoenfeld's residuals *P* value 0.25.
*The association between prednisone use and mortality approached the statistical significance (HR 1.41 95%CI 0.97–2.05 *P* value 0.07) after the exclusion of multimorbidity from the model.

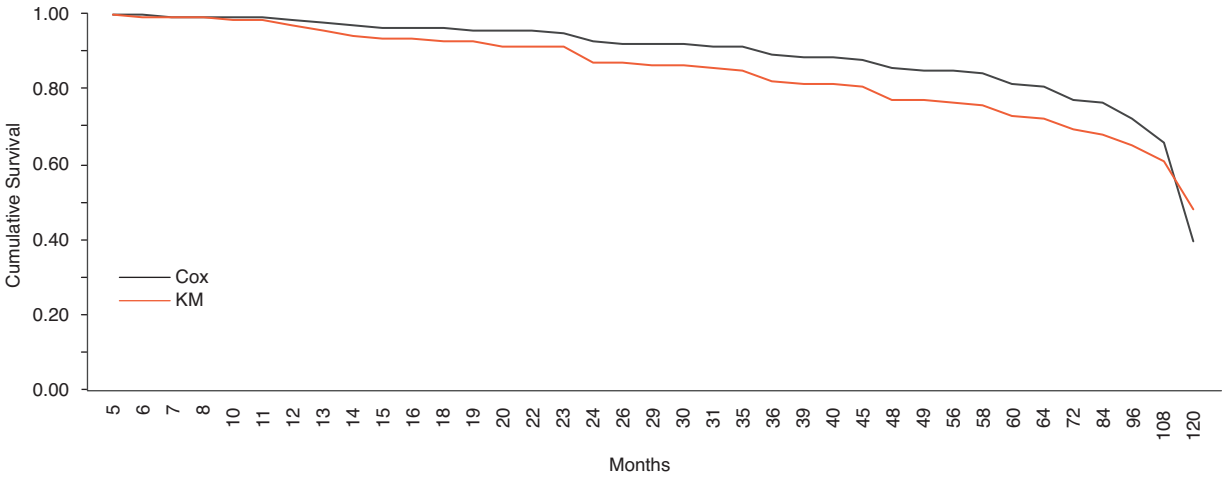

Figure 2 Cumulative survival curves of observed and fitted values.

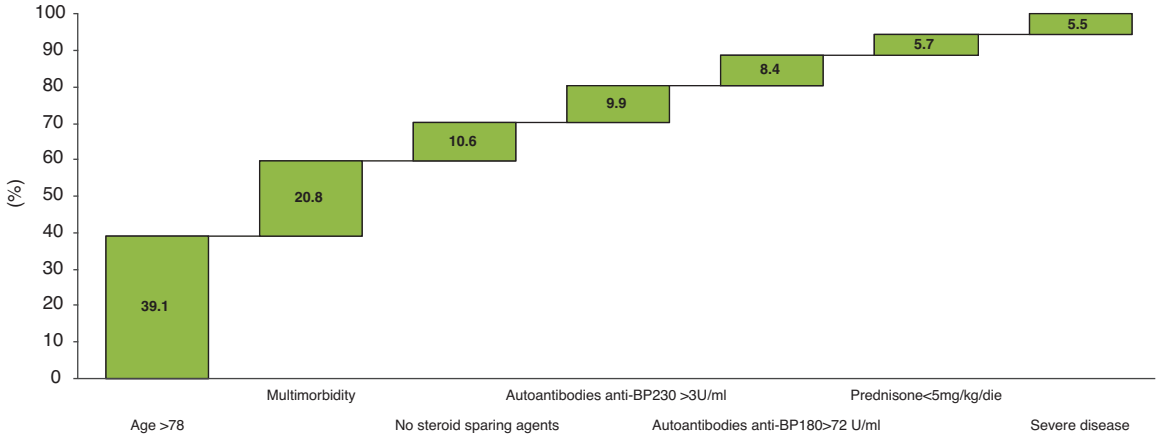

Figure 3 Risk score of death in patients with BP.

anti-BP230 > 3 U/mL, anti-BP180 > 72 U/mL, prednisone <0.5 mg/kg/day, and severe disease. To put this in perspective, an individual aged 79 years, with multimorbidity and anti-BP180 AAbs of 75 U/mL and no other risk factors among those included into the model, achieved a total risk score of 68.3% over a median time of observation of 35 months.

Discussion

In this multicentric nationwide retrospective study, we investigated the cumulative survival at 1, 3, 5 and 10 years and prognostic factors of BP patients in Italy for the first time, in a large cohort of patients. We found that a risk prediction model based on age, multimorbidity, sparing, anti-BP230 Aabs, anti-BP180 Aabs, prednisone, and disease severity provided 77% accuracy for predicting mortality in large series of Italian patients with BP.

BP and mortality

The reported worldwide mortality rates varied significantly according to various factors: geographical area, patient setting (hospitalized or outpatient subjects), and range of time considered (1 year, 3 years, 5 years, or more). In a recent meta-analysis[21] the authors concluded that the pooled estimate of 1-year mortality rate in BP patients is 23.5% worldwide. The stratified pooled estimate is higher in European cohorts than in American and Asian ones, although the heterogeneity between studies is large. Data on 3- and 5-year mortality are scarce. Some studies conducted in Switzerland, the United States, and Asia show the 3-year mortality ranging from 20% to 45% and the 5-year mortality ranging from 30% to 60.8%.[17,23–27]

In our population, the crude mortality rate was of 20.6%, with an incidence mortality rate of 5.9 × 100 person/year. The mortality rate at 1, 3, 5 and 10 years was 3.2%, 18.2%, 27.4% and 51.9%, respectively.

Compared with other studies, our sample had an overall lower mortality rate.[23,28,29] This result is likely due to the fact that the patients referred to the centers are outpatients, therefore in acceptable general conditions. The outpatient setting allows to reduce the risk of complications associated with hospitalization, particularly if longer, as reported in other studies.[30] In our experience, even the most complex patients (advanced age, multimorbidity, and/or severe disease), in presence of a good performance status, benefit more from outpatient management.

Mortality in BP and age

A large number of recent studies in the literature have shown a significant correlation between age and mortality in patients with BP. However, the age cut-off beyond which the increase in mortality becomes significant varied in these studies, ranging from 70 years to 80 years.[25,29,32]

In our sample, patients aged >78 years had increased mortality; therefore, our finding is in line with the literature.

Mortality in BP and multimorbidity

Another variable associated with increased mortality in most studies is the presence of comorbidities.

In qualitative terms, the comorbidities most frequently related with increased mortality rate are dementia,[30,24–32] stroke,[33] and Parkinson disease.[30]

In quantitative terms, having two or more comorbidities has been associated with higher mortality in several studies.[3,31] In our sample, we used the term multimorbidity as it was considered more appropriate, and a significant correlation between multimorbidity at the diagnosis of BP and higher mortality has been found.

Mortality in BP and immunological markers

The relationship between the presence of circulating AAbs against BP180/BP230 and mortality is a matter of debate in the literature.

Bernard *et al.*[8] in 1997 reported for the first time that the presence of circulating AAbs against BP180 was significantly more frequent in BP patients who died within the first year of treatment ($P < 001$). In recent years, Holtsche *et al.*,[4] showed that higher IgG anti-BP180 levels were associated with an increased 1-year mortality rate, and the presence of anti-BP230 IgG was more frequent in older patients (this finding had never been described before). Monshi *et al.*,[34] in a retrospective single-center study conducted in Vienna, identified a cut-off level of anti-BP180 AAbs at diagnosis (≥61 U/mL) beyond which mortality in the first year was higher. Also in our sample, anti-BP180 AAbs levels were found to be independent risk factors for death, if >72 U/mL. In addition, we identified a cut-off also in anti-BP230 AAbs, associated with higher mortality not only if >9 U/mL, but also if >3 U/mL. This is probably because in a selected population already diagnosed with BP, even an anti-BP230 AAbs value >3 U/mL was prognostically significant. This value, therefore, assumes a prognostic rather than diagnostic value in our population. As in the Holtsche *et al.*[4] study, we found that higher values were detected in older patients. The association between these AAbs and mortality risk had also been observed in the Italian single-center study we conducted.[35]

Our results corroborated the previous literature and provided a cut-off level of anti-BP180 and anti-BP230 AAbs, beyond which the risk of death is higher. These results support the growing evidence for the pathophysiological importance of anti-BP230 AAbs (surrogate markers for immunological "senescence", an altered epidermal structure in older patients) and also emphasize the importance of anti-BP180 AAbs as a prognostic factor, especially in combination with the former.

Table 4 Studies which investigated the influence of oral corticosteroids on mortality in patients with BP

Study	Country	Period of observation (years)	Mean age	Number of patients	Dosage of oral prednisolon (or equivalent)	Univariate analysis (*P*-value)	Multivariate analysis
Joly 2002[36]	France	1996-1998	81	341	1 mg/kg/die	0.02	
Rzany 2002[29]	Germany	1987-1997	77.3	369	>37.5 mg/die	0.001	HR 2.5 (1.5-4.3)
Cortes 2012[25]	Switzerland	1990-2003	79.5	60	≥ 40 mg/die	0.573	HR 1.17 (0.53-2.59)
Gual 2012[2]	Spain	1990-2010	77.8	101	≤ 10 mg/die > 10 mg/die	0.162 0.674	
Cai 2013[24]	Singapore	2004-2009	75.7	359	≤0.5 mg/kg/die > 25 mg/die > 30 mg/die	<0.001 0.09 0.83	HR 0.27 (0.14-0.32)
Li 2013[27]	China	1991-2011	64.3	140	> 65 mg/die > 42 mg/die	0.25 0.97	
Kalinska 2017[30]	Poland	2000-2013	76.2	205	0.5 mg/kg/die	0.03	HR 1.36 (0.79-2.34)
Rozenblat 2019[32]	Israel	2009-2016	79.1	87	-	0.46	
Monshi 2020[34]	Austria	2001-2012	81	100	80 mg/die	0.18	

In red colour, negative correlations between survival and oral steroids.
In green colour, positive correlations between survival and oral steroids.
In black colour, no significant correlation between survival and oral steroids.

Mortality in BP and oral corticosteroids

The risk–benefit ratio analysis of oral corticosteroid administration in the treatment of BP provided contradictory results in the literature.

In 2002, Joly *et al.*[36] conducted a prospective multicenter trial which demonstrated that prednisone administration at 1 mg/kg/day in patients with severe BP was associated with higher mortality rates than the application of topical steroid alone (clobetasol propionate cream). In this trial, 1-year mortality was 40%, and most of the causes of death were associated with adverse effects of steroid therapy, such as cardiovascular events, stroke, pneumonia, sepsis, hypertension, and diabetes. However, it should be pointed out that the dosage used by the French group corresponds to a high dose of prednisone and that this association was not then confirmed by the multivariate analysis. Since then, several other studies have been conducted on this topic, with controversial results (Table 4). More in detail, the multivariate analysis revealed a negative association between oral CS dosage and survival only in the study conducted by Rzany *et al.*[29] in which prednisone was administered at dosage >37.5 mg/day at discharge. In the remaining studies, this correlation was not confirmed, even when the CS dosage administered was moderate to high (>40 mg/day). In the Swiss study by Cortes *et al.*[25] a higher mortality rate was reported in patients receiving oral CS, but only when it was concomitant with the administration of chlorambucil.

On the contrary, the Singapore group study conducted by Cai *et al.*[24] investigated 359 patients and showed how patients treated with low-to-moderate doses of CS (<0.5 mg/kg/day of prednisone) had lower mortality than those taking doxycycline and/or nicotinamide, and this mortality was further reduced when these drugs were administered together. However, increasing the initial oral steroid dose correlated with decreased mortality in the multivariate analysis, up to the cut-off dose of 25 mg/day of prednisolone.

In our study, the proportion of patients on treatment with prednisone with a dosage <0.5 mg/kg/day was significantly higher ($P = 0.02$) in patients without (52%) than in those with (42%) multimorbidity, indicating that patients with a relatively better clinical profile were more frequently treated with the drug at that dose. Such an observation suggests that multimorbidity could act as a potential intermediate factor in the prednisone use-mortality link. In line with this hypothesis, data adjustment for multimorbidity could obscure the true effect of prednisone on mortality. To test this hypothesis, we performed an additional analysis by excluding multimorbidity from the multiple model (see legend to Table 3), and we found that the use of prednisone just failed to reach a statistically significant association (P 0.07) with mortality. The result of this multivariate modelling is compatible with the hypothesis of a potential intermediate role of multimorbidity in the prednisone use-death pathway. Furthermore, although with a statistical significance of 7%, our results suggest that a dosage of prednisone <0.5 mg/kg/day in the initial phase, and subsequent tapering, tends to be related with a higher risk of death, probably due to a late control of the disease and increased risk of complications.

An alternative explanation has emerged by studying the statistical association between lower corticosteroid dosages and presence of multimorbidity. This relation was found to be significant, so it is plausible that multimorbidity precludes full and sustained oral steroid treatment regimens and that it is due to multimorbidity in itself the highest risk of death.

Risk factor score in bullous pemphigoid

A novel finding emerged in our study is that a risk prediction rule based on simple risk factors such as age, multimorbidity, steroid-sparing drugs, prednisone use, and disease severity, jointly considered with two biomarkers routinely measured in clinical practice such as anti-BP230, anti-BP180, provided about 80% accuracy for predicting mortality in a large series of patients with BP. Furthermore, for the first time, we specifically assessed the additional prognostic value of anti-BP230 and anti-BP180 AAbs, and we found that these two biomarkers had a higher prediction value than that provided by steroids and disease severity (Fig. 3). The risk prediction rule developed in our study demands to be formally validated in an external independent cohort of BP patients to ascertain generalizability. Furthermore, our results represent a stimulus to design clinical study to demonstrate whether and at what extent a treatment strategy guided by the risk prediction rule proposed by us improves clinical outcomes in BP patients as compared to standard of care.

Conclusion

In conclusion, this study represents the first nationwide Italian study to have retrospectively investigated the mortality rates and prognostic factors in patients with BP.

Although the mortality tool seems to be effective in this cohort, it requires validation with an external cohort before implemented in clinical practice.

Main limitations are the retrospective nature and the mortality rates not adjusted for age, gender, and comorbidities of the general population, common limitations with other studies.[30,32]

On the other hand, the strengths are related to the large sample size and the inclusion of several centers, both in northern and southern Italy, resulting in more reliable data. Finally, the long median follow-up period allowed us to determine the mortality rate not only at 1 year, but also at 3, 5, and 10 years, and this represents an important support to the reliability of our findings.

Informed consent

The patients in this manuscript have given written informed consent to publication of their case details.

Data availability statement

DaThe data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Kaplan–Meier's survival table.

Appendix S2 Multivariate Cox model with standard value cut-off of BP230 (9 UI/mL).