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Outcome of patients with autoimmune diseases in the intensive care unit: a mixed cluster analysis

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ABSTRACT

Objectives: The interest on autoimmune diseases (ADs) and their outcome at the intensive care unit (ICU) has increased due to the clinical challenge for diagnosis and management as well as for prognosis. The current work presents a-year experience on these topics in a tertiary hospital.

Methods: The mixed-cluster methodology based on multivariate descriptive methods such as principal component analysis and multiple correspondence analyses was performed to summarize sets of related variables with strong associations and common clinical context.

Results: Fifty adult patients with ADs with a mean age of 46.7±17.55 years were assessed. The two most common diagnoses were systemic lupus erythematosus and systemic sclerosis, registered in 45% and 20% of patients, respectively. The main causes of admission to ICU were infection and AD flare up, observed in 36% and 24%, respectively. Mortality during ICU stay was 24%. The length of hospital stay before ICU admission, shock, vasopressors, mechanical ventilation, abdominal sepsis, Glasgow score and plasmapheresis were all factors associated with mortality. Two new clinical clusters variables (NCVs) were defined: Time ICU and ICU Support Profile, which were associated with survivor and no survivor variables.

Conclusions: Identification of single factors and groups of factors from NCVs will allow implementation of early and aggressive therapies in patients with ADs at the ICU in order to avoid fatal outcomes

KEY MESSAGES

- Morbidity and mortality in patients with autoimmune diseases seen at the intensive care unit (ICU) is still high.
- Infections and flare-up are major causes of ICU admission.
- Delay in ICU admission increases risk of mortality.
- Mixed-cluster analysis is a novel methodology establishing subgroups in real life.

INTRODUCTION

Autoimmune diseases (ADs) are chronic and heterogeneous conditions that affect specific target organs or multiple organ systems. These conditions share several clinical signs and symptoms, physiopathological mechanisms and genetic factors (ie, the autoimmune tautology).[1] Their incidence ranges from 1 to 20 cases per 100 000 person-years and the estimated prevalence is about 3%.[2] The impact of ADs resides in the high risk of morbidity and mortality they hold.[3] The chronic nature of these diseases places a significant burden on the use of healthcare resources, which translate into elevated economic costs and low quality of life compared with the general population.

Patients with ADs may be admitted to the intensive care unit (ICU), making them a challenge to the intensivist.[3–5] The prevalence of ADs in the ICU has changed in the past decades. In the past, the main ADs admitted to ICU, in order of frequency, were rheumatoid arthritis (RA), systemic lupus erythematous (SLE) and systemic vasculitis (SV). However, in the past decades SLE has been the most common AD reported.[5] Mortality of patients at the ICU has been shown to be variable, ranging from 17% to 55%.[5]

Although patients with ADs may have diverse causes of admission to the ICU, acute flare of the disease and infection, mainly due to immunosuppression, is the most important.[3–6] Since the expression of diseases varies depending on geography and ethnicity, and the information about ADs at the ICU in Latin America is scarce,[3 7–9] the aim of this study was to describe factors related to mortality during ICU stay in patients with ADs assessed in a single-centre in Bogota, the capital of Colombia.

MATERIALS AND METHODS

Study design

A retrospective case series review was performed from 1 February 2013 to 31 January 2014 for all adult patients with ADs evaluated by the Center for Autoimmune Disease Research (CREA) at the ICU in Mederi Hospital Universitario Mayor, a tertiary hospital in Bogota, Colombia. The hospital provides 828 beds, of which 120 are at the ICU (ie, medical, surgical, cardiac, neurological, others). The main general criteria for admission to the ICU are unstable conditions (ie, respiratory failure, haemodynamic collapse) or risk of an unstable condition. Every clinical record was fully evaluated to determine past medical history and outcome. Records of patients were systematically reviewed using a protocol that sought information on demographics, clinical and laboratory characteristics. Classification criteria were considered to include the following ADs: SLE, RA, SV, scleroderma (SSc), and Sjögren's syndrome (SS).[10–15] Dermatopolymyositis (DPM) was classified by using Dalakas and Hohlfeld criteria.[16] For antiphospholipid syndrome (APS) and autoimmune hepatitis (AIH), the 2006 updated classification criteria[17] and the international AIH group criteria[18] were used, respectively. In addition, other ADs were evaluated according to the respective classification criteria (ie, autoimmune thyroid disease, AITD).[19] For patients admitted more than once to ICU in the same hospitalisation, only the first ICU admission was considered.

Variables

The causes of ICU admission were classified as follows: (1) infection, (2) flare-up of AD, (3) complications derived from the underlying AD (ie, cardiovascular disease (CVD)), (4) adverse effects of immunosuppressors and (5) acute serious illnesses that were unrelated to the autoimmune condition. Infection was defined as a process characterised by an inflammatory response to the presence of micro-organisms (MOs) or the invasion of normally sterile host tissue by those MOs. Sepsis and septic shock were defined in accordance with the Surviving Sepsis Campaign Guidelines 2012.[20] ADs flare-up were defined as an exacerbation of a pre-existing AD condition.[21–26] Complications were acute serious illnesses that are altered or magnified by ADs. The acute conditions triggering ICU admissions were classified as follows: (1) respiratory failure, (2) haemodynamic collapse and (3) others (ie, postoperative, metabolic failure, neurological risk, risk of respiratory failure or haemodynamic collapse).

Other data recorded were age, gender, duration of disease, polyautoimmunity (ie, the presence of more than one AD in a single patient) including multiple autoimmune syndromes (MASs) when three or more ADs coexisted.[27–29] Comorbidities, immunosuppressors in the past 3 months, the time between hospital admittance and ICU admission (ie, length of hospital stay before ICU admission), length of ICU stay, the need of intensive care support (ie, mechanical ventilation (MV), vasopressor support, dialysis, plasmapheresis, blood transfusion) and the reduction in left ventricular ejection fraction using the definition available from American Heart Association for heart failure,[30] were also variables registered. Pulmonary hypertension corresponded to a pulmonary arterial systolic pressure >50 mm Hg measured by transthoracic echocardiography.[31] Abnormal acid–base blood balance was also recorded and dichotomised as normal or abnormal based on the Siggaard-Andersen nomogram.[32] The classification of Vincent *et al*[33] was used for shock. Other variables recorded were the Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[34] the organ dysfunctions and/or infection score,[35] the sequential organ failure assessment score (SOFA),[36] the PaO_2:FiO_2 ratio of arterial oxygen tension to inspired oxygen concentration according to the values for Acute Respiratory Distress Syndrome[37] and the Glasgow scale.[38] Finally, the treatment of AD during ICU was also registered.

Statistical analysis

The mixed-cluster methodology proposed by Lebart *et al*[39] based on multivariate descriptive methods such as principal component analysis and multiple correspondence analysis was performed to summarise sets of related variables with strong associations and common clinical context. Thus, by means of this clustering technique, for each set of related variables, new cluster variables (NCVs) were derived. For example, length of hospital stay before ICU admission and length of ICU stay, two variables with a non-linear relation, yielded a NCV (ie, 'Time ICU') which corresponds to a categorical variable with three outcomes (see results).

The χ^2 and Fisher's exact tests were performed to established differences between categorical variables (original and NCV) and mortality. Kruskal–Wallis test was performed for assessing possible differences in continuous variables on mortality status. Statistical analysis was performed in R 3.0.2.[40]

RESULTS

During the time period study (ie, February 2013 to January 2014), 485 hospitalised patients were evaluated by the CREA, of whom 79 were seen at the ICU. Of these, 50 were selected for analysis as they fulfilled the inclusion criteria of AD, the other 29 patients were excluded because they did not fulfil the classification criteria of AD.

Baseline patient characteristics are shown in table 1. Most of the patients were women (78%). The mean duration of ADs was 49.43±79.48 months (data were missing in three patients), and the mean length of stay in ICU was 10.96±11.06 days. The most frequent ADs were SLE, SSc and RA observed in 46%, 20% and 18%, respectively (table 2). There were 13 patients (26%) with

Table 1 Characteristics of patients with ADs admitted to the ICU

Characteristic	Total n=50	Survivors n=38 (76%)	No survivors n=12 (24%)	p Value	OR (95% CI)
Age (years)	*46.7±17.55*	*46.23± 18.58*	*48.17±14.39*	*NS*	
Gender, female (%)	39 (78%)	30 (78.9%)	9 (75%)	NS	
Length of hospital stay before ICU (days)	*6.82±9.61*	*4.65±8.13*	*13.67±11.03*	*0.002*	
Length of ICU stay (days)	*10.96±11.06*	*11.5±11.85*	*9.25±8.29*	*NS*	
Re-entry ICU	6 (12%)	5 (13.16%)	1 (8.33%)	NS	
Death during ICU stay	12 (24%)	–	–		
Death during hospitalisation after ICU	4 (8%)	4 (10.5%)	–		
Hospital readmission	5 (10%)	5 (13.2%)	–		
AD-related factors					
*Duration of AD (months)**	*49.43±79.48*	*47.75±84.79*	*54.91±62.02*	0.3822	
New diagnosis	11 (22%)	8 (22.2%)	3 (25%)	NS	
Previous comorbidity					
No disease background	16 (32%)	12 (31.6%)	4 (33.3%)	NS	
New diagnosis AD	5 (31.25%)	4 (33.3%)	1 (25%)	NS	
Previously diagnosis AD	11 (68.75%)	8 (66.7%)	3 (75%)	NS	
Cardio and cerebrovascular disease	18 (36%)	15 (39.5%)	3 (25%)	NS	
Chronic kidney disease	13 (26%)	12 (31.6%)	1 (8.3%)	NS	
Prior immunosuppressant within 3 months					
No pharmacology background	15 (30%)	12 (31,6%)	3 (25%)	NS	
Steroids	33 (66%)	24 (63.2%)	9 (75%)	NS	
Other immunosuppressors†	22 (44%)	15 (39.5%)	7 (58.3%)	NS	
ICU parameters					
APACHE II (n=42)	*14.07±7.02*	*13.53±7.47*	*15.8±5.25*	0.2737	
ODIN score	*2.48±1.57*	2.26±*1.52*	3.18±*1.59*	0.1041	
Glasgow score	*12.94±3.21*	*13.65±2.48*	*10.67±4.21*	*0.043*	
Severe Glasgow score‡	*7 (14%)*	*2 (5.26%)*	*5 (41.6%)*	*0.005*	11.5 (1.71 to 77.18)
Complication during ICU stay§	7 (14%)	2 (5.3%)	5 (41.7%)	*0.002*	7.50 (1.97 to 57.96)
MV	26 (52%)	15 (39.5%)	11 (91.67%)	*0.002*	7.91 (1.88 to 71.61)
# days MV	*4.24±8.49*	*3.53±8.53*	*6.5±8.32*	0.037	
Dialysis	11 (22%)	10 (26.3%)¶	1 (8.3%)	NS	
CPR	13 (26%)	2 (5.3%)	11 (91.7%)	$<10^{-4}$	66.0 (13.30 to 948.89)
Transfusion	35 (70%)	24 (63.2%)	11 (91.7%)	NS	
Vasopressor support	26 (52%)	16 (42.1%)	10 (83.3%)	0.013	4.31 (1.25 to 26.14)
Shock	26 (52%)	16 (42.1%)	10 (83.3%)	0.013	4.31 (1.25 to 26.14)
Alveolar haemorrhage	10 (20%)	9 (23.7%)	1 (8.3%)	NS	
IVIG ICU	19 (38%)	16 (42.1%)	3 (25%)	NS	
Plasmapheresis ICU	10 (20%)	5 (13.2%)	5 (41.7%)	0.031	3.44 (1.07 to 18.52)
ICU support NCV (n=38)**	14 (36.8%)	3 (11.5%)	11 (91.6%)	$<10^{-4}$	31.63 (6.70 to 395.34)
Infections					
Sepsis	33 (66%)	24 (63.2%)	9 (75%)	NS	
Septic shock	18 (36%)	11 (28.9%)	7 (58.3%)	NS	

Continued

Table 1 Continued

Characteristic	Total n=50	Survivors n=38 (76%)	No survivors n=12 (24%)	p Value	OR (95% CI)
With no pharmacology background††	9 (27.28%)	6 (25%)	3 (25%)	NS	
With pharmacology background‡‡	24 (72.72%)	18 (75%)	6 (66.7%)	NS	
Urinary sepsis§§	19 (38%)	14 (36.8%)	5 (41.6%)	NS	
Lung sepsis§§	10 (20%)	7 (18.4%)	3 (25%)	NS	
Abdominal sepsis	5 (10%)	1 (2.63%)	4 (33.3%)	*0.002*	8.22 (1.80 to 97.04)

The continuous variables are represented with mean±SD and the categorical variables are represented with frequency (percentage); p value presented corresponds to survivor and no-survivor comparison.
*Data not available for three patients.
†Other immunosuppressors (ie, DMARDs, antimalarial, azathioprine, cyclophosphamide, mycophenolate mofetil, anti-TNF).
‡Severe Glasgow score was defined as a score of ≤8 in Glasgow during ICU admission.
§Complications during ICU stay excluding infection or AD.
¶Hospital discharge with dialysis in seven patients (18.4%).
**Need any of ICU support grouped in clusters: ICU support G1 compared with ICU support G3.
††Those are the patients with sepsis who does not have rheumatological pharmacology background in the past 3 months.
‡‡Patients with any rheumatological pharmacology background in the past 3 months.
§§One patient has two source of sepsis (urinary and lung).
¶¶Time related with ICU stay: G1 compared with G3 (see Figure 1).
AD, Autoimmune disease. APACHE II, Acute Physiology and Chronic Health Evaluation II score. CPR, cardiopulmonary resuscitation. DMARDs, Disease-modifying antirheumatic drugs. ICU, Intensive care unit. IVIG, intravenous IgG; MV, Mechanical ventilation; NCV, new cluster variable; NS, not significant; ODIN, organ dysfunctions and/or infection; TNF, tumour necrosis factor.

polyautoimmunity, of whom 4 (8%) had MAS. Eleven patients were newly diagnosed as having AD during hospitalisation.

Twelve patients (24%) did not survive during ICU stay and their causes of death were sepsis in five, intracerebral haemorrhages in two and upper gastrointestinal bleeding, cardiac tamponade and hemoperitoneum secondary to kidney biopsy in each one. In two patients the cause of death was not determined.

Sixteen patients (32%) did not have a previous comorbidity. Conversely, 13 patients (26%) had chronic kidney disease and 18 patients (36%) had CVD. Most of the patients were on steroids (n=33 (66%)). Otherwise, disease-modifying antirheumatic drugs (DMARDs) were registered in nine patients (18%), antimalarial in eight patients (16%), immunosuppressors (ie, azathioprine, cyclophosphamide, mycophenolate mofetil) in eight (16%), and three (6%) patients were on anti-tumour necrosis factor drugs (ie, adalimumab, etanercept and infliximab, respectively).

Infection was the most frequent (36%) cause of admission. Thirteen patients presented with septic shock as the cause of ICU admission (table 2). Total sepsis events were observed in 33 patients (66%). Seventeen patients become infected after ICU admission, and five patients developed septic shock after ICU admission. Urinary tract infection and pneumonia were the most frequent infections observed during ICU stay, and were the most frequent cause of sepsis (38% and 20%, respectively). Abdominal sepsis was registered in five cases (ie, gastrointestinal and gynaecological), of which four cases were associated with urinary tract infection and pneumonia. Two cases had infective endocarditis. Septicaemia without identifiable source was registered in two cases. In summary, 21 patients had one source of sepsis and 12 patients had two sources of sepsis due to different MOs.

The use of intravenous IgG (IVIG) and plasmapheresis was more frequent than the use of immunosuppressors (ie, cyclophosphamide and anti-CD20 monoclonal antibodies) as treatment for disease flare-ups.

Factors associated with poor outcome (ie, death) were length of hospitalisation before entry to ICU, low Glasgow scores and length of MV (table 1). In the survivor group, seven patients (18.4%) were discharged on haemodialysis and four patients (10.5%) deceased after ICU discharge. Five patients (13.2%) were readmitted to the hospital before 30 days of discharge.

Two significant NCVs where found. First NCV was 'Time ICU' derived from length of hospital stay before ICU admission and length of ICU stay variables, which provided in turn three groups (figure 1). The second NCV was 'ICU support profile', derived from cluster analysis on outcomes of MV, non-invasive MV, cardiopulmonary resuscitation, vasopressor support, transfusion and dialysis variables. From this NCV, four groups where obtained (figure 2).

For these two NCV we found that in Time ICU-G1 (short total ICU stay and long hospital stay before ICU

Table 2 Reasons of AD admission to ICU

Characteristic	Total (n=50)	Poly AD (n=13)	SLE (n=23)	SSc (n=10)	RA (n=9)	APS (n=6)	SV (n=7)	DPM (n=3)	SS (n=3)	AIH (n=2)	AITD (n=3)	PEN (n=2)	PRS (n=1)
Infection	18 (36)	5 (38.46)	10 (45.45)	3 (30)	5 (55.56)	2 (33.3)	1 (16.67)	–	1 (33.33)	1 (50)	–	–	–
AD flare-up	12 (24)	2 (15.38)	3 (16.64)	1 (10)*	–	–	4 (57.4)	3 (100)	1 (33.33)	1 (50)	–	1 (50)	1 (100)
AD complication	10 (20)	3 (23.08)	3 (13.64)	4 (40)	1 (11,11)	2 (33.3)	–	–	1 (33.33)	–	2 (66.66)	1 (50)	–
Adverse drug effect	2 (4)	1 (7.69)	–	1 (10)†	1 (11.11)	1 (16.67) †	1 (16.67)†	–	–	–	–	–	–
Not related to AD‡	8 (16)	2 (15.38)	7 (30.43)	1 (10)	2 (22.22)	1 (16.67)	1 (16.67)	–	–	–	1 (33.33)	–	–

*Polyautoimmunity was the cause of admission in SSc due to flare up of SLE.
†Cause of admission due to warfarin over-anticoagulation in a patient with polyautoimmunity. There were 50 patients with at least one AD; from this group 13 patients (26%) presented at least one other AD (ie, polyautoimmunity). A total of 69 ADs were reported and the cause of ICU admission related with kind of ADs. All patients with AD met the international classification criteria.[22]
‡Infection excluded.
AD, autoimmune disease; AIH, Autoimmune hepatitis; AITD: autoimmune thyroid disease; APS, Antiphospholipid Syndrome; DPM, dermatopolymyositis; PEN, immunological cytopenia (autoimmune haemolytic anaemia, primary immune thrombocytopenia); PRS, pulmonary renal syndrome; RA, Rheumatoid Arthritis; SLE, Systemic Lupus Erythematosus; SS, Sjögren syndrome; SSc, Systemic Scleroderma; SV, systemic vasculitis.

admission) was associated with a higher risk of death in relation to Time ICU-G3 (short hospital stay before ICU and during ICU). Although this finding is explained by the association between mortality and long hospital stay before ICU admission (see table 1), this cluster analysis shows an interesting relation between total ICU stay and hospital stay before ICU admission. There were no patients with long duration on both variables. Patients in our study disclosed a long hospital stay before ICU admission and short ICU stay or vice versa. Similarly, ICU support-G1 (high presence of all the studied supports except non-invasive MV and dialysis) was associated with higher risk of death in relation to ICU support-G3 (little support needed) (table 1).

DISCUSSION

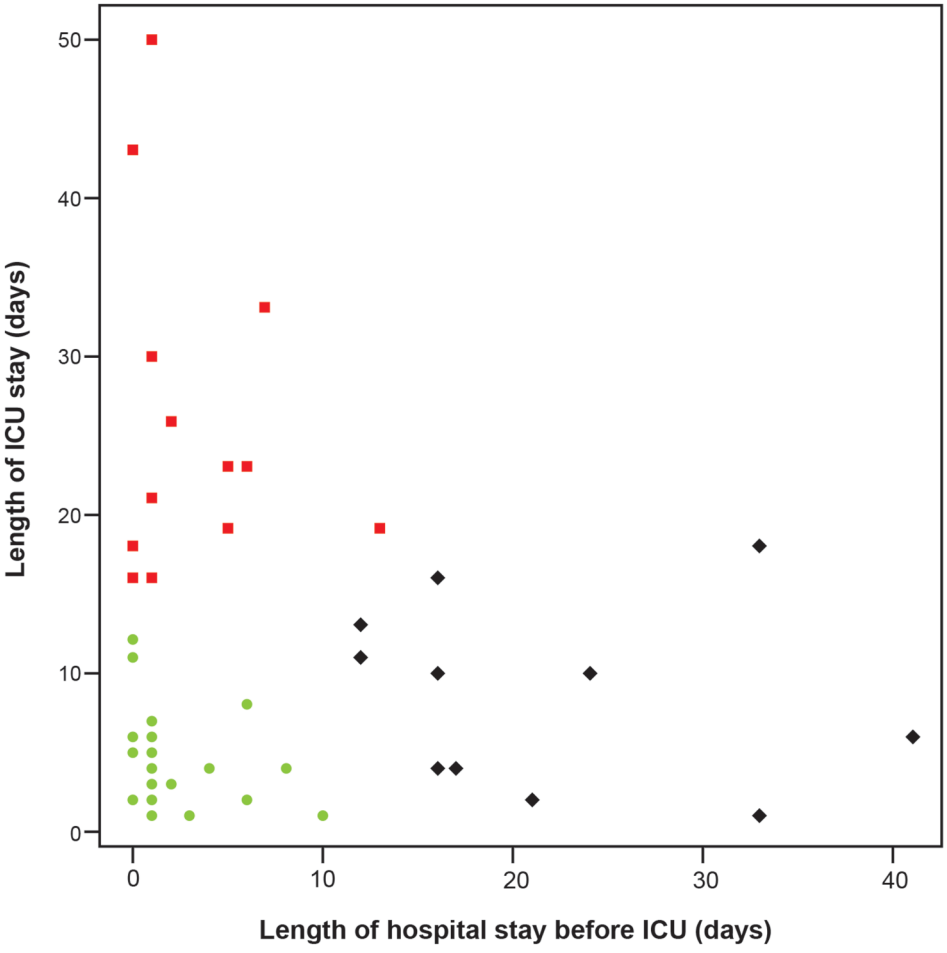
The present study shows the 1-year characteristics and a mixed-cluster analysis of patients with ADs who required admittance to the ICU in a referral hospital in Bogota, Colombia. The most common diagnosis in our series was SLE, as has been already reported.[3 7 8] However, the second AD was SSc, a result differing from previous studies.[3 6–8 41] Although polyautoimmunity was frequently registered (26%), no significant influence of this condition on outcome was observed in this study. Our results indicate that in spite of the great progress on ICU resources and a better understanding of autoimmunity, there is still a high morbidity and mortality in patients with ADs seen at the ICU.

Known factors associated with mortality in patients with ADs admitted to the ICU are APACHE II, SOFA, length of stay, shock, comorbidities, vasopressors or immunosuppressive drugs.[3 6 7 41–44] In our case series, the length of hospital stay before ICU admission, shock, vasopressors, MV, abdominal sepsis, Glasgow score and plasmapheresis were all factors associated with mortality.

Noteworthy, instead of considering each variable separately, we introduce the construction of NCVs as a novel methodology with the goal of establishing relevant clinical variables present together in a patient, since clinical manifestations do not appear isolated but rather in conjunction with others. With this approach, subgroups are identified allowing clinicians to better manage patients in real-life conditions.[45]

Previous studies and ours have identified that long hospital stay before ICU admission is a survival risk factor for patients with ADs.[5 43] A delay in recognising patients with unstable conditions may worsen their survival rate. Thus, it is important to establish early detection programmes to identify patients at risk of mortality.[20]

The ICU support profile NCV disclosed four groups and represents life support manoeuvres (figure 2) used in the ICU. Some of these manoeuvres were already evaluated as individual variables; however, this analysis represent the interaction of groups of life support and the needed of life support due to organ failure (ie,



Group 1	Higher	Days before ICU admission
	Lower	Days in ICU
Group 2	Higher	Days in ICU
	Lower	Days before ICU admission
Group 3	Lower	Days before ICU admission; Days in ICU

Figure 1 New cluster variable Time ICU. Within this cluster, three groups are observed, namely G1, G2 and G3. G1 was characterised by a short total ICU stay and long hospital stay before ICU admission. G2 had an opposite trend of that found in G1, that is, long total ICU stay and short hospital stay before ICU admission. Finally, G3 was related with short hospital stays before ICU and during ICU. Total days in ICU refers to the length of stay at ICU regardless the number of re-entries; Days before ICU admission refers to the length of hospital stay before ICU admission. ICU, Intensive care unit.

worst prognosis).[3 42 44 46] Plasmapheresis is a valuable treatment option for critically ill patients suffering antibody-mediated illness such as ADs and has been considered a relatively safe treatment of ICU patients.[47 48] In the present case series plasmapheresis was associated with mortality, denoting severity of illness. Thus, this association should be considered as a bias (ie, confounding by indication).

Comorbidities in patients with ADs should be recognised as early as possible and treated promptly in the hope of avoiding systemic complications.[3–5 49] Some important comorbidities such as CVD and chronic renal disease have a bad impact on the quality of life, patients' survival and, as expected, increases the economic burden of disease.[50] Nevertheless, in the present study comorbidities were not associated with mortality.

Previous works (table 3) have reported an ICU mortality ranging from 17% to 55%.[3 6–8 41 42 44 46 50–53] In our study, the mortality rate was 24%, being one of lowest. Infections have ranged from 27% to 64%, and the flare up from 23% to 54%. These two are the main causes of ICU admission.[3 6–8 41 42 44 46 50–53] Infection is favoured by immunosuppressive treatment and the immune response abnormalities inherent of ADs[54–56] and may be developed in the community.[57] An infection should always be ruled out at the time an AD flare-up is considered.[3–5]

We would like to acknowledge the limitations of our study. Long-term survival of patients which has been related with a decrease in quality of life, disability and higher costs[58 59] was not considered in the present work. In fact, four patients included in the total analysis died during the same hospitalisation once discharged from

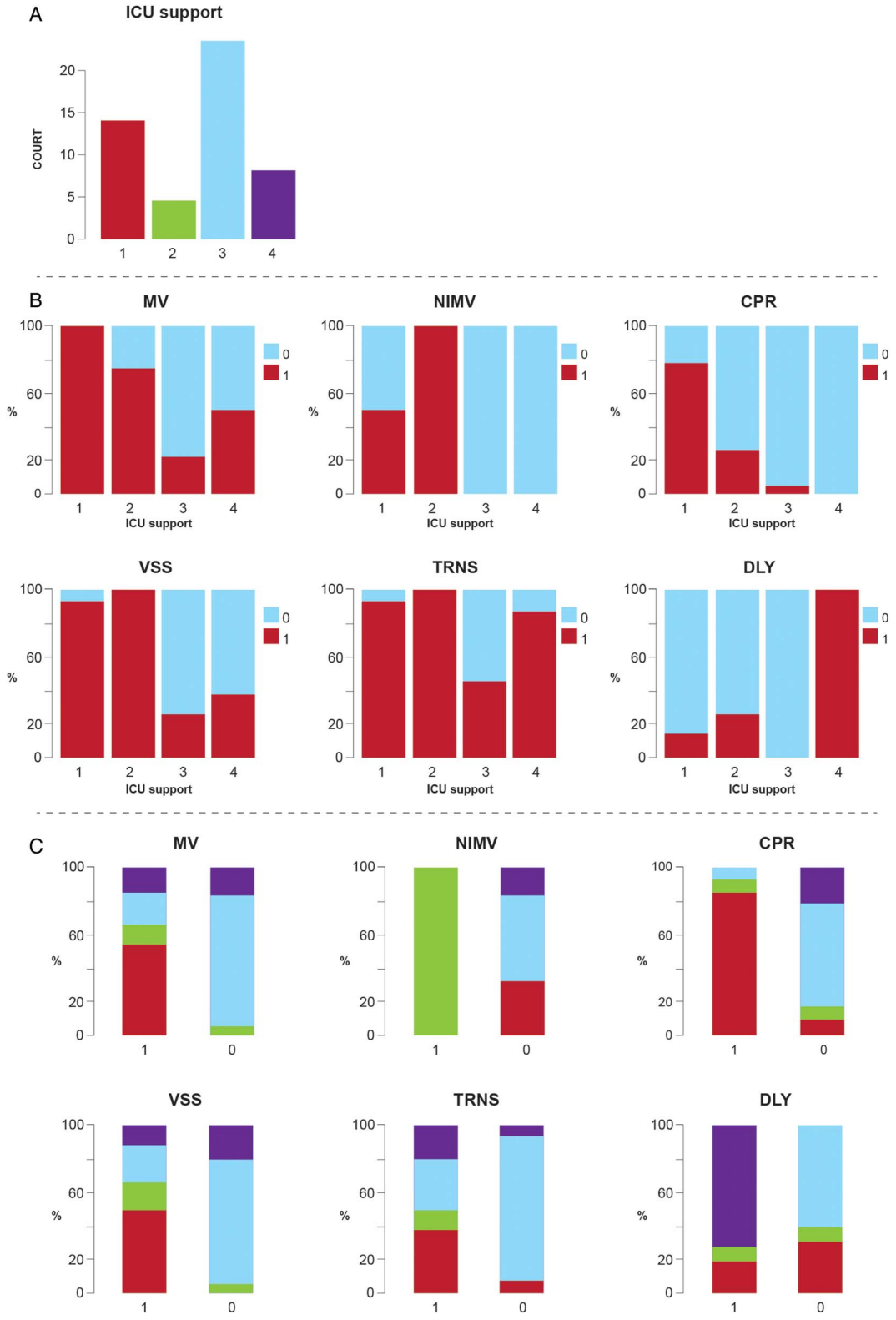


Figure 2 'ICU support profile' cluster. From this new cluster variable, four groups where obtained (A): (1) ICU support-G1, associated with high presence of all the studied supports except non-invasive mechanical ventilation and some sporadic dialysis; (2) ICU support-G2, associated with high presence of all the studied supports except CPR and DLY; (3) ICU support-G3, related with patients for whom little if any support was needed, and (4) ICU support-G4, associated with those patients requiring DLY and transfusion together with very few outcomes in other supports. (B) Profile of each group with respect to the original variables used to build the groups. (C) Profile of each original variable in terms of groups' composition. 1: presence of the variable, 0: absence of the variable. CPR, cardiopulmonary resuscitation; MV, mechanical ventilation; NIMV, non-invasive MV; VSS, vasopressor support; TRNS, blood transfusion; DLY, dialysis.

Table 3 ADs at the ICU (revision of the literature)

Author (reference)	Year	No.	In-ICU mortality (%)	Infection (%)	AD flare-up (%)	AD complication (%)	Adverse drug effect (%)	Not related to AD (%)
Godeau *et al*[50]	1992	69	33	42	28	NR	NR	17
Kollef *et al*[41]	1992	36	31	NR	NR	NR	NR	NR
Bouachour *et al*[46]	1996	88	38	31	32	NR	NR	23
Godeau *et al*[6]	1997	181	33	41	28	NR	18	13
Pourrat *et al*[51]	2000	33	30	33	26	NR	NR	NR
Thong *et al*[44]	2001	28	54	64	NR	NR	NR	NR
Moreels *et al*[41]	2003	71	32	30	NR	NR	NR	NR
Camargo *et al*[3]	2005	24	17	38	38	29	17	25
Coral *et al*[8]	2006	18	55	27	44	22	5	NR
Cavallasca *et al*[7]	2010	31	55	35	23	NR	NR	13
Anton *et al*[53]	2012	37	19	32	54	NR	NR	NR
Faguer *et al*[52]	2013	149	16	47	48	NR	NR	11
Current study	2014	50	24	36	24	20	4	16

NR, not reported.

the ICU unit and were not consider into the ICU non-survivor group. Sample size precludes any inference of causality in the links between ICU mortality and related factors. Despite the meticulous study design, which was employed to control for confounding factors, the relation between plasmapheresis and non-survival could be attributed to confounding by indication due to hospital protocol.

CONCLUSION

We report a novel analysis of the outcome of patients with ADs admitted to the ICU. Detection of single factors and groups of factors from NCVs will allow implementation of early and aggressive therapies in order to avoid fatal outcomes.

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REFERENCES

1. Anaya J-M, Shoenfeld Y, Rojas-Villarraga A, *et al*., eds. *Autoimmunity from bench to bedside*. Editorial Universidad del Rosario. Bogotá, 2013.
2. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev* 2003;2:119–25.
3. Camargo J, Tobón G, Fonseca N, *et al*. Autoimmune rheumatic diseases in the intensive care unit: experience from a tertiary referral hospital and review of the literature. *Lupus* 2005;14:315–20.
4. Janssen NM, Karnad DR, Guntupalli KK. Rheumatologic diseases in the intensive care unit: epidemiology, clinical approach, management, and outcome. *Crit Care Clin* 2002;18:729–48.
5. Quintero OL, Rojas-Villarraga A, Mantilla RD, *et al*. Autoimmune diseases in the intensive care unit. An update. *Autoimmun Rev* 2013;12:380–95.
6. Godeau B, Mortier E, Roy PM, *et al*. Short and long-term outcomes for patients with systemic rheumatic diseases admitted to intensive care units: a prognostic study of 181 patients. *J Rheumatol* 1997;24:1317–23.
7. Cavallasca JA, Del Rosario Maliandi M, Sarquis S, *et al*. Outcome of patients with systemic rheumatic diseases admitted to a medical intensive care unit. *J Clin Rheumatol* 2010;16:400–2.
8. Coral P, Diaz M, Chalem M, *et al*. Outcome of patients with rheumatic diseases that requires attention in the medical intensive care unit. *J Clin Rheumatol* 2006;12:S77–8.
9. Cairoli E. Unidades de enfermedades autoinmunes sistémicas: notas de una experiencia en curso. *Rev Médica Urug* 2013;29:248–9.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
11. Van den Hoogen F, Khanna D, Fransen J, *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013;65:2737–47.
12. Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
13. Vitali C, Bombardieri S, Jonsson R, *et al*. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554–8.
14. Jennette JC, Falk RJ, Bacon PA, *et al*. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013;65:1–11.
15. Hunder GG, Arend WP, Bloch DA, *et al*. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Introduction. *Arthritis Rheum* 1990;33:1065–7.
16. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet* 2003;362:971–82.
17. Miyakis S, Lockshin MD, Atsumi T, *et al*. International consensus statement on an update of the classification criteria for definite

antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306.
18. Hennes EM, Zeniya M, Czaja AJ, *et al*. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology* 2008;48:169–76. 10
19. Rojas-Villarraga A, Toro CE, Espinosa G, *et al*. Factors influencing polyautoimmunity in systemic lupus erythematosus. *Autoimmun Rev* 2010;9:229–32.
20. Dellinger RP, Levy MM, Rhodes A, *et al*. Surviving sepsis campaign: International Guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580–637.
21. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. Systemic Lupus Erythematosus Disease Activity Index 2000. *J Rheumatol* 2002;29:288–91.
22. Prevoo M, van't Hof M, Kuper H, *et al*. Modified disease activity scores that include twenty-eight—joint counts. *Arthritis Rheum* 1995;38:44–8.
23. Bose N, Chiesa-Vottero A, Chatterjee S. Scleroderma renal crisis. *Semin Arthritis Rheum* 2015;44:687–94.
24. Alexanderson H, Lundberg IE. Disease-specific quality indicators, outcome measures and guidelines in polymyositis and dermatomyositis. *Clin Exp Rheumatol* 2007;25(6 Suppl 47):153–8.
25. Ramos-Casals M, Tzioufas AG, Stone JH, *et al*. Treatment of primary Sjögren syndrome: a systematic review. *JAMA* 2010;304:452–60.
26. Rodríguez-Pintó I, Soriano A, Espinosa G, *et al*. Catastrophic antiphospholipid syndrome: an orchestra with several musicians. *Isr Med Assoc J* 2014;16:585–6.
27. Anaya JM. The diagnosis and clinical significance of polyautoimmunity. *Autoimmun Rev* 2014;13:423–6.
28. Rojas-Villarraga A, Amaya-Amaya J, Rodriguez-Rodriguez A, *et al*. Introducing polyautoimmunity: secondary autoimmune diseases no longer exist. *Autoimmune Dis* 2012:2012:254319.
29. Anaya JM, Castiblanco J, Rojas-Villarraga A, *et al*. The multiple autoimmune syndromes. A clue for the autoimmune tautology. *Clin Rev Allergy Immunol* 2012;43:256–64.
30. Yancy CW, Jessup M, Bozkurt B, *et al*. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;128: e240–319.
31. Galiè N, Hoeper MM, Humbert M, *et al*. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the Internat. *Eur Heart J* 2009;30:2493–537.
32. Siggaard-Andersen O. Acid-base balance. In Encyclopedia of Respiratory Medicine, 2005:1–6.
33. Vincent J, De Backer D. Circulatory shock. *N Engl J Med* 2013;369:1726–34.
34. Knaus W, Draper E, Wagner D, *et al*. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13:818–29.
35. Fagon J, Chastre J, Novara A, PM, *et al*. Intensive Care Medicine Characterization of intensive care unit patients using a model based on the presence or absence of organ dysfunctions and/or infection: the ODIN model. *Intensive Care Med* 1993;19:137–44. 11.
36. Moreno R, Vincent J, Matos R, *et al*. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. *Intensive Care Med* 1999;25:686–96.
37. Ranieri VM, Rubenfeld GD, Thompson BT, *et al*. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307:2526–33.
38. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. *Lancet* 1974;13:81–4.
39. Lebart L, Morineau A, Piron M. *Statistique exploratoire multidimensionnelle*. Paris, Dunod; 1995.
40. R Development Core Team. R: a language and environment for statistical computing. 011.
41. Kollef MH, Enzenauer RJ. Predicting outcome from intensive care for patients with rheumatologic diseases. *J Rheumatol* 1992;19:1260–2.
42. Moreels M, Mélot C, Leeman M. Prognosis of patients with systemic rheumatic diseases admitted to the intensive care unit. *Intensive Care Med* 2005;31:591–3.
43. Alzeer AH, Al-Arfaj A, Basha SJ, *et al*. Outcome of patients with systemic lupus erythematosus in intensive care unit. *Lupus* 2004;13:537–42.
44. Thong BY, Tai DY, Goh SK, *et al*. An audit of patients with rheumatic disease requiring medical intensive care. *Ann Acad Med Singapore* 2001;30:254–9.
45. Van der Esch M, Knoop J, van der Leeden M, *et al*. Clinical phenotypes in patients with knee osteoarthritis: a study in the Amsterdam osteoarthritis cohort. *Osteoarthr Cartil* 2015;23:544–9.
46. Bouachour G, Roy PM, Tirot P, *et al*. [Prognosis of systemic diseases diagnosed in intensive care units]. *Presse Med* 1996;25:837–41.
47. Paton E, Baldwin IC. Plasma exchange in the intensive care unit: a 10 year retrospective audit. *Aust Crit Care* 2014;27:139–44.
48. Szczeklik W, Wawrzycka K, Włudarczyk A, *et al*. Complications in patients treated with plasmapheresis in the intensive care unit. *Anaesthesiol Intensive Ther* 2013;45:7–13.
49. Amaya-Amaya J, Montoya-Sánchez L, Rojas-Villarraga A. Cardiovascular involvement in autoimmune diseases. *Biomed Res Int* 2014;2014:367359.
50. Godeau B, Boudjadja A, Dhainaut J, *et al*. Outcome of patients with systemic rheumatic disease admitted to medical intensive care units. *Ann Rheum Dis* 1992;51:627–31.
51. Pourrat O, Bureau JM, Hira M, *et al*. [Outcome of patients with systemic rheumatic diseases admitted to intensive care units: a retrospective study of 39 cases]. *Rev Med Interne* 2000;21:147–51.
52. Faguer S, Ciroldi M, Mariotte E, *et al*. Prognostic contributions of the underlying inflammatory disease and acute organ dysfunction in critically ill patients with systemic rheumatic diseases. *Eur J Intern Med* 2013;24:e40–4.
53. Anton JM, Castro P, Espinosa G, *et al*. Mortality and long term survival prognostic factors of patients with systemic autoimmune diseases admitted to an intensive care unit: a retrospective study. *Clin Exp Rheumatol* 2012;30:338–44.
54. Doria A, Canova M, Tonon M, *et al*. Infections as triggers and complications of systemic lupus erythematosus. *Autoimmun Rev* 2008;8:24–8.
55. Avcin T, Canova M, Guilpain P, *et al*. Infections, connective tissue diseases and vasculitis. *Clin Exp Rheumatol* 26(1 Suppl 48): S18–26.
56. Girschick HJ, Guilherme L, Inman RD, *et al*. Bacterial triggers and autoimmune rheumatic diseases. *Clin Exp Rheumatol* 26(1 Suppl 48):S12–7. 12
57. Ortiz G, Dueñas C, Rodríguez F, *et al*. Epidemiology of sepsis in Colombian Intensive care units. *Biomedica* 2014;34:40–7.
58. Pandharipande PP, Girard TD, Jackson JC, *et al*. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013;369:1306–16.
59. Wilcox ME, Brummel NE, Archer K, *et al*. Cognitive dysfunction in ICU patients: risk factors, predictors, and rehabilitation interventions. *Crit Care Med* 2013; 41(9 Suppl 1):S81–98.