

The main limitation of this study is that we may have generated some bias by limiting inclusion to patients referred to a bronchoscopy unit, as this procedure might not be requested in all patients; metastasis of the underlying tumor perhaps being assumed in many cases.

In conclusion, the appearance of mediastinal lymphadenopathies in patients with extrapulmonary tumors should not be assumed to be tumor recurrence, and other causes, including sarcoidosis, must be considered. Histological diagnosis is the technique of choice in these cases. Although the relationship between cancer and sarcoidosis and the pathogenic mechanisms that might link them have not been clearly established, either the tumor itself or else the anticancer treatment may possibly promote the development of sarcoidosis in genetically predisposed individuals. More studies are needed to clarify this association and its clinical value and prognosis.

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## Risk Stratification in Chronic Obstructive Pulmonary Disease: Can the Spanish Guidelines be Improved?\*

### Estratificación de riesgo de la enfermedad pulmonar obstructiva crónica. ¿Se puede mejorar la propuesta de la guía española?

To the Editor:

The risk stratification of patients in the 2017 edition of the Spanish COPD guidelines (GesEPOC)<sup>1</sup> is simpler than that in the first edition.<sup>2</sup> Although the multidimensional indices, BODE and BODEX, have shown good ability to predict mortality, they are rarely used in clinical practice. For this reason, the new GesEPOC guidelines propose a dichotomous stratification of high and low risk, according to the presence or absence of three risk factors: FEV<sub>1</sub><50%, mMRC functional dyspnea grade >2 (or = 2 in patients already receiving bronchodilators), and a history of exacerbations. It occurred to us that a quantitative classification that took into account the number of risk factors present in each patient could offer advantages with respect to the dichotomous classification, allowing patients to be classified into escalating risk categories, in a similar manner to the

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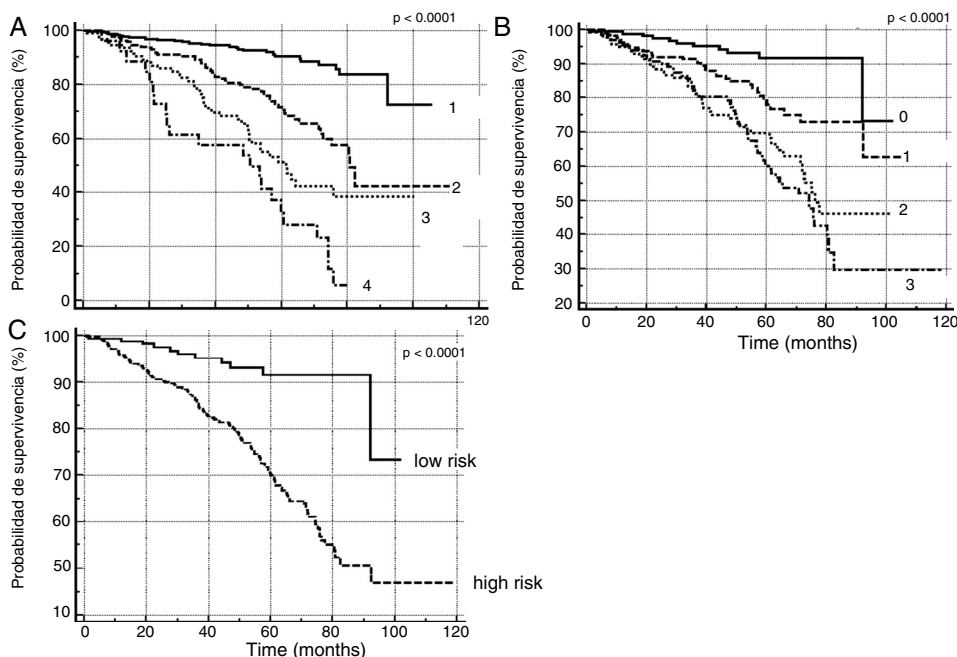
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BODE/BODEX indices, while being easier to apply in clinical practice than stratification based on multidimensional indices.

In order to verify this hypothesis, we performed a retrospective study of all patients seen in the dedicated COPD clinic of a university hospital. The study population comprised all consecutive patients with a diagnosis of COPD according to the GOLD initiative criteria<sup>3</sup> and a history of smoking (cumulative exposure >10 pack-years), seen between January 2008 and April 2017 (726 subjects). The patients were selected from a healthcare database in which body mass index, lung function, mMRC functional grade (with and without treatment), history of exacerbations in the year prior to the index date (date of the first clinic visit), and moderate (requiring treatment with antibiotics or steroids) or severe exacerbations (requiring attention in the emergency room or admission) were systematically recorded. Patients were classified according to: (1) a quantitative scale using BODEX index quartiles<sup>2</sup> (2) the high–low risk dichotomous scale recommended by GesEPOC 2017,<sup>1</sup> and (3) a 4-level quantitative scale, on the basis of the number of risk factors present in each patient (0, 1, 2 or 3). We performed a survival analysis for the three scales according to the Kaplan–Meier method, using the log-rank test for the comparison of survival curves. A Cox's proportional hazards analysis was performed, using age and comorbidity measured by the Charlson index as covariates. We compared the ability of the two quantitative scales to predict overall mortality using receiver operator curves (ROC), comparing the areas with the Delong method.<sup>4</sup>

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**Figure 1.** Kaplan–Meier curves for the severity scales. (A) BODEx index quartiles. (B) Number of GesEPOC-2017 risk criteria. (C) Dichotomous low risk/high risk classification according to GesEPOC 2017.

Patients were excluded due to missing study variables (59), or because they were lost to follow-up (30), followed up for <6 months (25), or underwent lung transplantation (4). Study population: 667 subjects, 597 men (89.5%); age:  $68.3 \pm 9.5$  years; FEV<sub>1</sub> %:  $49.9 \pm 17.2$ . SpO<sub>2</sub>:  $93.1 \pm 4.6$ %. Patients with SpO<sub>2</sub> <90%: 115 (17.2%). BMI:  $28.2 \pm 15.1$  kg/m<sup>2</sup>. Classification by severity of airflow obstruction: GOLD 1, 36 (5.3%); GOLD 2, 292 (43.7%); GOLD 3, 246 (36.8%); GOLD 4, 93 (13.9%). BODEx:  $2.6 \pm 1.9$ . Patients with Charlson index >1: 319 (47.8%). Follow-up time:  $47.9 \pm 23.8$  months. In total, 490 subjects (73.4%) were classified as high risk according to GesEPOC 2017 (215 subjects had a single risk factor, 143 had 2, and 132 had 3 risk factors). There were 149 deaths (22.3%), within a mean of  $39.0 \pm 22.4$  months after the first visit.

Fig. 1 shows the Kaplan–Meier curves for the three severity scales. In all cases, the different scores obtained from the scales allowed groups with different mortality risks to be identified ( $P < 0.0001$  for comparison of survival curves). Table 1 shows the results of the Cox analysis for the risk factor scale, which maintained its predictive value after correcting for potential confounding factors. The area under the ROC curve for classification by BODEx index quartiles (0.78, 95% CI: 0.75–0.81) was greater than the quantitative classification by risk factors (0.71, 95% CI: 0.68–0.75) (difference: 0.07, 95% CI: 0.03–0.09,  $P < 0.0001$ ).

Our study has limitations, and serves essentially to generate a hypothesis and stimulate scientific debate. Being a retrospective study, the risk of selection bias is obvious, as it was performed in a dedicated hospital clinic. Indeed, a very large number of patients were at high risk. Moreover, the study was not validated externally in an independent group. Nevertheless, the results suggest that a quantitative classification according to the number of risk factors present in each patient may have advantages over the dichotomous classification proposed by GesEPOC 2017, as subjects are classified according to escalating categories of risk of mortality that could guide intensification of treatment. This classification is more intuitive, and easy to apply in all areas of care, so it might achieve greater acceptance than the scale based on multidimensional

**Table 1**

Results of the Cox's proportional hazards multivariate analysis for the scale by number of GesEPOC 2017 risk factors, adjusted for age and comorbidity.

Variable	HR (95% CI)	P
Age	1.03 (1.01–1.05)	0.0001
Charlson index	1.32 (1.20–1.45)	<0.0001
One risk factor*	2.35 (1.19–4.61)	0.01
Two risk factors*	4.03 (2.09–7.80)	<0.0001
Three risk factors*	4.39 (2.29–8.42)	<0.0001

HR: hazard ratio.

\* The group with no risk factors is the reference.

severity indices. We must point out that there is no evidence to show that establishing several levels of risk could have therapeutic implications that translate to clinical outcomes. Our study also shows that classifying severity on the basis of multidimensional indices is more useful for predicting mortality, so such an approach is still recommendable in the settings in which it can realistically be applied. We report these results in the hope that they are of interest to specialists who manage COPD patients, although the potential application of the severity scale we propose, or of other alternatives, in decision-making would require an adequate external validation performed across the spectrum of disease severity.

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## Methotrexate Pneumonitis in Crohn's Disease: A Rare Case Report and Review of Literature



### Neumonitis por metotrexato en la enfermedad de Crohn: un caso clínico inusual y revisión de la literatura

Dear Editor:

Methotrexate (MTX) is an analog of folic acid with antiproliferative and immunomodulating effects.<sup>1</sup> Low-dose MTX therapy is a well-recognized treatment for various inflammatory diseases, including rheumatoid arthritis, psoriatic arthritis, psoriasis, and inflammatory bowel disease.<sup>2</sup> More than 20 years ago, the clinical efficacy of MTX was also established for steroid-dependent Crohn's disease (CD).<sup>3</sup> Pulmonary toxicity is a rare side effect of MTX, which clinically is characterized by the new onset of dyspnea, dry cough, and fever and usually presents radiologically as an acute interstitial pneumonitis.<sup>4</sup> Pneumonitis is a serious and unpredictable adverse event of treatment with MTX that may become life-threatening.<sup>5</sup> Since the first description in 1969,<sup>6</sup> Imokawa et al.<sup>7</sup> collected 123 cases of MTX-induced pneumonitis published in the English language literature and added the description of 9 further cases. Cancer and leukemia were the underlying diseases in most patients (64.4%) followed by psoriasis (7.6%) and rheumatoid arthritis (6.1%). However, no case of pneumonitis associated with MTX therapy in patients with CD was identified in this clinical series. We here describe the case of a woman with ileocecal CD who presented with pneumonitis after 10 months of treatment with MTX. In a review of the literature, we were able to collect only three cases of MTX-induced pneumonitis in patients with CD,<sup>8–10</sup> although one of these cases has been published twice.<sup>8,11</sup> A review of salient clinical findings of CD patients with MTX-induced pneumonitis is also presented.

A 79-year-old woman was followed up at the Gastroenterology Service of our hospital since 2011 when CD was diagnosed. The patient presented with an acute episode of intestinal occlusion and underwent diagnostic and therapeutic laparotomy. An inflammatory stenosing mass of 4 cm in diameter, located at 25 cm of the ileocecal valve was found and excised. Histological examination of the surgical specimen confirmed the diagnosis of CD. Postoperatively, the patient started treatment with azathioprine but it was withdrawn shortly after because of symptoms of intolerance. Therapeutic options were discussed with the patient, and treatment with MTX at doses of 25 mg per week subcutaneously was initiated. The drug was well tolerated and complete remission of the disease was achieved. Ten months after starting treatment with MTX, she was admitted to the hospital because of persistent dry cough and dyspnea, which have been present for one month. There was no history of fever or alteration of her general condition. Physical examination was unrevealing and routine laboratory studies including blood cell count, liver and renal function tests, and biochemical profile with serological tests and antibodies against main pulmonary pathogens were in the normal range. The sputum was negative including bacteria, mycobacteria, viruses, and fungi. Chest roentgenogram did not disclose abnormal findings. A high-resolution chest CT scan showed diffuse parenchymal ground-glass opacities with subpleural reticulation, predominantly in the upper

lobe of the right lung (Fig. 1). Bronchoscopy was negative, with absence of malignant cells in the cytological examination and no evidence of bacterial, viral, mycobacterial, or fungal infections in cultures. MTX-related toxicity was suspected, and treatment was discontinued. High dose oral steroids were given and clinical symptoms promptly improved. At 3 months after MTX withdrawal, a high-resolution CT scan was normal. The patient was then treated with 6-mercaptopurine and budesonide for 3 months. Budesonide was then discontinued and the patient is currently maintained on clinical remission with 6-mercaptopurine monotherapy.

Since preliminary data published in 1989<sup>6</sup> showing that MTX had some efficacy for the treatment of patients with refractory inflammatory bowel disease,<sup>12</sup> evidence supports the view that MTX is a useful alternative in patients with active CD unresponsive to standard immunosuppressive drug treatment.<sup>13</sup> MTX at dose of 25 mg/week is effective at inducing remission and in allowing steroid tapering for steroid-refractory or steroid-dependent patients with CD.<sup>14</sup> Bone marrow suppression, nausea, vomiting, hepatic fibrosis, and lung toxicity are potential adverse effects associated with low dose MTX therapy, and have been mostly documented in patients with rheumatoid arthritis.

Lung toxicity due to MTX in patients with CD treated with this drug has been exceptionally reported, with only three previous cases published in the literature.<sup>8–10</sup> All patients were women, aged between 36 and 69 years, and presented with dyspnea and non-productive cough, with restrictive respiratory insufficiency in one patient.<sup>8</sup> Also, treatment with MTX was indicated in the context of severe colitis, ileo-colitis or ileo-pancolitis in steroid-dependence or intolerance to infliximab or azathioprine. The time elapsed between the initial dose of MTX and presenting symptoms was short (2 and 10 days) in two cases<sup>8,10</sup> after 18 months of drug administration in one case<sup>9</sup> and after 10 months in our patient. Diagnosis was made by the presence of ground-glass opacities on chest CT. Elevated cell counts (lymphocytes, eosinophils) were noted on bronchoalveolar lavage in two cases.<sup>8,10</sup> Alarcon et al.<sup>15</sup> identified risk factors for MTX pneumonitis in patients with rheumatoid arthritis, including older age, diabetes, rheumatoid pleuropulmonary involvement previous use of disease-modifying antirheumatic drugs, and hypoalbuminemia. Older age represents the strongest predictor of lung injury, the risk being double in 50–59 year-old patients and six-fold in patients over 60 years-old.<sup>15</sup> The patient reported by Trivedi et al.<sup>10</sup> was 64 years-old, and our patient was 69 years-old. However, neither diabetes nor hypoalbuminemia or pre-existing pulmonary diseases were presented in CD patients with MTX pneumonitis. All these cases met diagnostic criteria for MTX pneumonitis.<sup>11</sup> In our patient, the diagnosis of MTX-induced pneumonitis can be considered unequivocal according to the radiologic evidence of pulmonary interstitial infiltrates, the negative blood cultures (major criteria 2 and 3) in conjunction with 3 minor criteria (shortness of breath for <8 weeks, non-productive cough, and normal leukocyte count [ $<15,000$  cells/mm<sup>3</sup>]). A complete resolution of pneumonitis was observed by CT scan at 3 months after MTX withdrawal and a course of systemic steroids. In the routine daily practice, diagnosis can be established by a compatible clinical history, radiological images of ground-glass opacities, and presence of lymphocytes and/or eosinophils and increased CD4/CD8 ratio in BAL samples. Lung biopsy is rarely