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EXTENDED ABSTRACT

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Cox Models and Cure Mixture Models – An application to the time to hospitalization in Ulcerative Colitis patients

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Introduction

Ulcerative colitis (UC) is an idiopathic chronic inflammatory bowel disease characterized by periods of remission and acute exacerbations, and unpredictable disease course. Despite the availability of new drugs, there are still a considerable proportion of patients that will be refractory to therapy, need colectomy or develop complications, highlighting the need for better predictive markers of disease course [1].

Considering the endoscopic extent of disease at the time of diagnosis, patients were divided into three major subgroups: inflammation limited to the rectum (E1), left-sided colitis with inflammation distally to the splenic flexure (E2) and extensive colitis with involvement proximal to the splenic flexure (E3). The combination of endoscopy and histology seem to provide a better indication of disease activity than endoscopy alone, especially in endoscopically non-inflamed mucosa. No study has assessed the prognostic value of histological features at diagnosis, and therefore it remains unknown whether the pre-treatment microscopic findings can predict the course of the disease.

Herein, we designed a multicenter retrospective study to evaluate the prognostic value of histologic features in treatment-naïve proctitis and left-sided ulcerative colitis patients. Our goals were to evaluate the prevalence of microscopic inflammation in the macroscopically uninflamed mucosa, as well as the predictive value of the histological features of disease (in the endoscopically inflamed and non-inflamed mucosa) at the time of diagnosis.

In Portugal there has been a considerable consumption of medical resources associated to UC. Between 2010 and 2017, around 3400 people were hospitalized due to this disease, with an average hospital stay of 10 days with a minimum of 0 days and a maximum of 109 days, making the study of hospitalizations in this disease is a very relevant issue in order to have a perspective of its occurrence, as well as to help in the monitoring of patients and in clinical and hospital administration decision making. In this work, we analyse the time to the need of hospitalization of 93 patients diagnosed with UC in stages E1 and E2.

Methods

Cox models were used since proportional hazards assumption was not rejected and Cox models are popular amongst medical researchers, especially concerning the parameter interpretation [2]. Moreover, according to [3], a good discrimination among parametric models require censoring not to exceed 40-50 per cent. Our data is of moderate size and about 85% of the cases correspond to censored times. Nevertheless, for comparison purposes, we consider fitting parametric models in future work since they can perform better than the Cox model if the conditions they require are met.

Results

Age, endoscopic extent and severity scores at diagnosis on the time to hospitalization were the considered covariates. From these, only age was significantly associated, with older individuals being expected to have later hospitalizations (HR 0.95 (CI 95%: 0.9-0.99), p-value=0.016). As said above, a large proportion of individuals had no hospitalizations despite their long disease history. The observed mean time to hospitalization was 1.34 years (0.02 - 3.31 years) whereas the average time of censured observations was 4.33 years (0.18 - 26.95 years), suggesting that there are individuals who will never experience the event of interest, even if the time under observation could be prolonged indefinitely. Therefore, we considered the possible existence of "healed to hospitalization" individuals. To explore this hypothesis, cure

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models were implemented considering the same set of covariates for comparison purposes [4]. It is assumed that the individuals come from a mixture of two populations – those who will experience a hospitalization and those who will not. Besides producing an estimate of the probability of "cure", it is expected to obtain a more realistic estimate of the survival function for the fraction of the population who will suffer the event.

In the component concerning the susceptibility, the only relevant variable was Nancy score (OR=4.36; CI 90% (1.09,17.4); p-value=0.08), with higher level of Nancy score favouring susceptibility. None of the variables showed relevance to describe the failure time. A simpler model, considering only the Nancy score as covariate, was also estimated. Results were consistent with the former model (OR=4.35; CI 90% (2.54,12.7); p-value=0.024). The estimated cure rates are of 94.8% and 80.9% for patients with Nancy score <3 and ≥ 3 respectively, indicating that a very high percentage of the patients will never experience hospitalization. Regarding the failure time part of the model, although Nancy score presented a smaller p-value when compared to the previous model, still it was not significant.

Discussion and Conclusions

Comparing the results of both models made us believe that to disregard the possibility of "cure" may lead to biased conclusions concerning the influence of the considered covariates in the time to hospitalization.

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