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Fabiana Cazzorla

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**STUDY ON THE RELATIONSHIP BETWEEN NUTRITIONAL STATUS
AND INFECTION WITH ENTEROBACTERIACEAE PRODUCING
EXTENDED-SPECTRUM BETA-LACTAMASES (ESBL-E)**

THÈSE
POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE
SPÉCIALITÉ : SANTÉ PUBLIQUE

Par Mme Fabiana CAZZORLA

[Données à caractère personnel]

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Abréviations et acronymes

ESBL-E: Extended-spectrum beta-lactamases producing *Enterobacteriaceae*

CHU GA: Centre Hospitalier Grenoble Alpes

MICE: Multiple imputation by Chained equation

OR: Odds ration

CI: confidence interval

PREDIMED: Plateforme de Rassemblement et d'Exploitation des Données bloMEDicales, health data hub

IL-1 : interleukin-1

IL-6 : interleukin-6

TNF- α : Tumour Necrosis Factor alpha

USA : Uniated States of America

MRB: Multi drug resistant bacteria

HAS: High Authority for Health

BMI: Body Mass Index

MNA: Global Mini Nutritional Assessment

SD: standard deviation

IQR: median and interquartile range

Titre : Étude sur la relation entre l'état nutritionnel et l'infection à Entérobactéries productrices de Bêta Lactamases à Spectre Elargi (E-BLSE)

Résumé

Introduction

Les entérobactéries productrices de bêta-lactamases à spectre élargi (E-BLSE) sont de plus en plus répandues dans les établissements de santé. La dénutrition est connue comme facteur qui augmente d'environ 400% le risque d'acquérir une infection, mais son association spécifique avec les infections à E-BLSE n'a pas été étudiée.

Objectif

Analyser la relation entre dénutrition chez des patients hospitalisés et la présence d'une d'infection à E-BLSE.

Méthodes

Nous avons mené une étude cas témoins appariée, rétrospective, chez des patients majeurs hospitalisés au CHU Grenoble Alpes entre janvier 2010 et décembre 2018 qui ont présenté une infection à Entérobactéries. Les cas présentaient une infection à E-BLSE et les témoins une infection à entérobactéries non productrices de BLSE. Nous avons utilisé les critères de dénutrition de 2019 définis par la Haute Autorité de Santé pour identifier le critère d'exposition. Les facteurs de risque connus d'infection à E-BLSE ont été inclus : antécédent de prescription d'antibiotiques, antécédent d'hospitalisation, actes à risque, antécédent de colonisation à E-BLSE.

Les données des patients ont été collectées grâce à l'entrepôt de données de santé de l'hôpital PREDIMED. Les données manquantes ont été modélisées avec la technique d'imputation multiple par équation enchaînée (MICE) et les Odds Ratios (OR) ont été calculés à l'aide d'une régression logistique conditionnelle.

Résultats

Nous avons inclus **6 218 patients** dans notre étude : **2 099 cas** et **4 119 témoins**. Au moins un facteur propre au statut nutritionnel était évaluable pour 4 583 patients (73,7%). Selon le modèle d'imputation MICE, l'**OR brut de la dénutrition était de 1,10 (IC 95% 0,92-1,32)**. Après ajustement sur les autres facteurs de risque d'infection à E-BLSE, l'Odds Ratio ajusté (aOR) pour la dénutrition est resté similaire (**aOR = 1,11 [IC 95% 0,86-1,43]**). Les facteurs connus de risque d'infection à E-BLSE tels que les procédures invasives (aOR = 2,24 [IC95% 1,70-2,96]), l'antécédent d'hospitalisation (aOR = 1,76 [IC95% 1,51-2,06]), l'antécédent de prescription d'antibiotiques (aOR = 4,49 [IC95% 3,31-6,09]), la colonisation précédente par E-BLSE (aOR = 12,45 [IC95% 8,40-18,45]) et la durée de séjour préalable à l'infection (médiane de 4,62 jours chez les cas et 2,49 jours chez les témoins, $p < 0,05$) ont été mis en évidence.

Conclusion

À notre connaissance, notre étude est la première à étudier spécifiquement la relation entre la dénutrition et le risque d'infection à E-BLSE. L'utilisation de l'entrepôt de données PREDIMED a permis une collecte extensive de données informatiques, mais une grande proportion de données manquait pour estimer le statut nutritionnel. Pour exploiter pleinement l'entrepôt de données, une amélioration de la traçabilité des données des patients est nécessaire. La mise en place d'une étude prospective pourrait permettre un recueil exhaustif de la dénutrition et améliorer la précision des résultats.

Abstract

Introduction

Enterobacteriaceae producing Extended-Spectrum Beta-Lactamases (ESBL-E) are increasingly prevalent in healthcare settings. Malnutrition is a known risk factor for infectious diseases, but its association with ESBL-E infection is not well studied.

Aim of the study

We aimed to investigate the relation between malnutrition and the risk of ESBL-E infection.

Methods

We conducted a retrospective matched case-control study with patients hospitalised in Grenoble Alpes University Hospital between 1st January 2010 and 31st December 2018 with Enterobacteriaceae positive clinical sample. Cases presented an infection with ESBL-E and controls an infection with non-producing ESBL-E. We used the 2019 criteria for malnutrition set by the French healthcare authority and collected data on various risk factors related to ESBL-E infection (previous hospitalisation, invasive procedures, previous antibiotic use and previous colonisation with ESBL-E). Patients' data were collected through the hospital health data warehouse PREDIMED. Missing data were modelized with the Multiple Imputation by Chained Equation (MICE) technique and Odds Ratios (OR) were calculated with conditional logistic regression.

Results

We included **6,218 patients** in our study, consisting of **2,099 cases** and **4,119 controls**. At least one factor on nutritional status was evaluable on 4,583 patients (73.7%). According to the MICE model of imputation, **the crude OR was 1.10 (95% CI 0.92-1.32)**. After adjusting for other risk

factors of ESBL-E infection, the adjusted OR (aOR) for malnutrition remained similar (**aOR=1.11, 95% CI 0.86-1.43**). Significant risk factors of ESBL-E were identified as invasive procedures (aOR=2.24 [CI95% 1.70-2.96]), previous hospitalisations (aOR=1.76 [CI95% 1.51-2.06]), previous use of antibiotics (aOR=4.49 [CI95% 3.31-6.09]), previous colonisation by ESBL-E (aOR=12.45 [CI95% 8.40-18.45]) and the length of stay prior to infection (a median of 4.62 days in case group and 2.49 days in control group, $p < 0.05$).

Conclusion

To our knowledge, our study is the first to specifically investigate the relationship between malnutrition and the occurrence of ESBL-E infections. The use of the **PREDIMED** data warehouse allowed for extensive collection of informatic data but still a large proportion of data was missing to estimate nutritional status. In order to fully exploit the data warehouse, an **improvement in traceability** of patients' data is necessary to reduce missing data. Moreover, a **prospective study could be developed** for systematic collection of malnutrition criteria and avoid missing data.

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Introduction

Antibiotic resistance is a significant issue in public health. Bacteria become multi-resistant to antibiotics when they accumulate acquired resistance to several families of antibiotics, leaving them only sensitive to a limited number of antibiotics that can still be used in treatment. In France in 2016, the number of incident cases in diagnostic samples of Extended-Spectrum Beta-Lactamases producing Enterobacteriaceae (ESBL-E) was 15,267, with 9% of them found in blood cultures and 70% in urinary samples¹. In France, according to a survey conducted in healthcare facilities by Santé Publique France, the French national public health institution, 15.33% of all tested Enterobacteriaceae strains were ESBL producers, with a proportion of patients with ESBL-E infection of 0.27%, and this percentage has not decreased in recent years². Furthermore, mortality rate for invasive healthcare-associated infections (HAI) attested at 18% for *Escherichia coli* producing ESBL². At the Grenoble Alpes University Hospital (CHU GA), a systematic surveillance of ESBL-E infections has been carried out by the infection control department since 2007. In 2020, the number of positive diagnostic samples for ESBL-E was 404 (5% of the total number of samples).

Factors increasing the risk of being colonized with ESBL-E are not clear, except for the previous use of antibiotics³. Regarding infections caused by ESBL-E, two known risk factors are the use of antibiotics and pre-existing colonization with ESBL-E^{3,4}. Long-term hospitalization or stays in nursing homes are also associated with a high prevalence of ESBL-E infections, as for invasive procedures (mechanical ventilation, urinary catheter, arterial or venous catheter) and previous hospitalisations⁴⁻⁷.

Malnutrition increases the risk of nosocomial infections by 400% in elderly hospitalized patients⁸ and recent data show that malnutrition affects almost 70% of hospitalized patients in nursing homes and healthcare facilities⁹. This population is generally multimorbid, more susceptible to infections, and have often been hospitalized multiple times. The impact of nutritional status on the immune system has already been demonstrated, as it can result in the deregulation of metabolic pathways, including those involving IL-1, IL-6, TNF- α , and leptin¹⁰. An example in elderly population is the phenomenon called "inflamm-aging,"^{11,12} characterized by the alteration of the microbiota as a consequence of the chronic inflammatory state that commonly occurs in older individuals. Furthermore, there is already an evidence on African paediatric population of an augmented risk of ESBL-E bacteraemia in malnourished infants⁷. Several animal studies have already shown that a dietary change determines a change in the microbiota¹³, and currently there is a study in USA underway to investigate the correlation between fibre intake and the presence of different Multi Resistant Bacteria (MRB)¹⁴. Achieving a satisfactory nutritional status is dependent upon the proper absorption of essential proteins and calories required for optimal bodily function during daily activities. Failing to adhere to this fundamental principle may lead to the development of protein-energy malnutrition, which can be detrimental to individual health status. In France, the High Authority for Health (HAS) produced in 2019 new definitions of malnutrition based on phenotypic and etiological criteria^{15,16}.

Hypothesis

To our knowledge, no study has yet investigated the causal relationship between nutrition and susceptibility to infections caused by MRB. We hypothesize that malnutrition represents a risk factor for the acquisition of ESBL-E infections and in our study, we aim to evaluate this

relationship. If the relation is confirmed, the identification of malnutrition in a patient could provide an early indication to screen for MRB colonization and implement appropriate infection control measures, as well as adjust the antibiotic therapy.

Objectives

The main purpose of this study was to evaluate whether an association exist between malnutrition status (established by HAS criteria) and the presence of ESBL-E infection in the population of hospitalized patients at CHU GA.

After adjusting on risk factors associated with the presence of ESBL-E infection, the relation between malnutrition status and ESBL-E infection was evaluated. Additionally, this relation was investigated in a sub-population of patients without any known potential risk factors for ESBL-E infection.

The innovation of this study is based on the evaluation of the patient's nutritional status using PREDIMED (Platform for the Collection and Exploitation of Biomedical Data), the Health Data Warehouse of CHU GA¹⁷. PREDIMED is based on a modular, scalable, and powerful architecture, offering secure storage and processing of distributed data. This platform offers big data tools to explore all available data quickly and easily, as well as new possibilities for analysing this data.

Materials and Methods

Study design, setting and study period

We conducted a retrospective case-control study with adult patients hospitalized for at least 48 hours at the CHU GA. The inclusion period last 9 years between 1st January 2010 and 31st December 2018.

The CHU GA is the reference university hospital of the Isère department (France) and serves a population of 675,000 inhabitants with 2,133 hospital beds and places, and a total of 555,368 hospitalization days in 2018.

Outcomes definition

The primary outcome was the crude Odds Ratio (cOR) of malnutrition exposure in patients infected with ESBL-E compared to those infected with non-producing ESBL-E. Secondly, adjusted OR (aOR) for identified risk factors were calculated using a conditional multivariate logistic regression model. The same analysis were conducted in the sub-population without any potential risk factors.

Study population

Every adult patient who was admitted to the CHU GA during the study period and had a positive diagnostic sample for *Enterobacteriaceae*, was eligible to be included in the study.

Cases population was represented by patients with a diagnostic positive sample for ESBL-E. Controls were represented by patients with a diagnostic positive sample for non-producing ESBL-E. Each case was then matched with 1 or 2 controls based on age (+/- 5 years), sex, year of admission, and bacteria.

Given the multiplicity of samples per patient over the long period considered, we chose to give priority to ESBL-E samples. Then, for each patient, the first sample within the inclusion period was selected. If multiple bacteria were found in the same sample, the first microorganism presented in the laboratory report was selected. Due to the large number of microorganisms that can be present in a single sample, the choice to match on a single bacterium may constitute a bias. However, this choice was motivated by the frequency of bacterial infections in hospital settings¹⁸ (with *E. coli* and *Klebsiella pneumoniae* being the most common), and by the different clinical severity of some microorganisms. For example, *E. coli* ESBL is more frequently associated with invasive infections compared to *K. pneumoniae* ESBL^{19,20}.

Susceptibilities against antimicrobial agents and the ESBL production was routinely detected by the disc diffusion method using antibiotic discs of cefepime, cefotaxime and ceftazidime placed at a distance of 30 mm around a disc of clavulanic acid as recommended by the Antibiogram Committee of the French Microbiology Society²¹.

Exposure criteria

Exposure criteria, malnutrition, was defined according to the 2019 HAS criteria¹⁵.

For the **adult population < 70 years old**, malnutrition is defined by the presence of at least 1 phenotypic and 1 etiological criterion. Phenotypic criteria included weight loss ($\geq 5\%$ in 1 month or $\geq 10\%$ in 6 months or $\geq 10\%$ compared to usual weight before the onset of the disease), Body Mass Index (BMI) $< 18.5 \text{ kg/m}^2$ and quantified reduction in muscle mass and/or muscle function.

The etiological criteria included a reduction of food intake ($\geq 50\%$ for more than 1 week, or any reduction in food intake for more than 2 weeks), reduced absorption

(maldigestion/malabsorption), state of aggression (protein hyper catabolism with or without inflammatory syndrome, acute or chronic evolving pathology or evolving malignant pathology).

For the **elderly population (≥ 70 years)**, malnutrition is defined by the presence of at least one phenotypic criterion. It included weight loss ($\geq 5\%$ in 1 month or $\geq 10\%$ in 6 months), BMI < 21 kg/m², Albumin level < 35 g/L and Global Mini Nutritional Assessment (MNA) score < 17 .

This study, focused on the hospital population, enables us to validate the etiological criterion (acute or chronic progressive pathology or progressive malignant pathology) for adults < 70 years old and facilitates the collection of exposure data.

Collected variables

Demographic information, such as age and sex, was gathered for each patient, along with details of their hospitalization, including bacterial sampling and antibiograms (ESBL-E colonization was noted up to 12 months before infection), length of the hospital stay, length of stay prior to infection and prescription of antibiotics at CHU GA (within 6 months prior to hospitalization). Furthermore, any previous hospitalizations at CHU GA within 12 months before the current hospitalization was investigated.

In addition, the Charlson Comorbidity Index²² was calculated based on comorbidities listed in the patient's medical records. Invasive procedures were also identified, including the use of vascular catheters, urinary catheters, or artificial ventilation during the index hospitalization before the *Enterobacteriaceae* infection.

Measures related to malnutrition criteria, such as weight (collected at 1 and/or 6 months during hospitalization), height, BMI (calculated using the weight measurement closest to the date of sampling), and albuminemia (g/L), were also collected. The most relevant value for

each variable was selected based on specific time frames and delays (see Table 1a in the appendix).

All data were extracted through the PREDIMED data warehouse, which queried data from various software programs used in the hospital (Cristal link, Diane, Easily).

Statistical analyses

Number of subjects required

The required sample size was calculated based on the primary outcome measure. With two controls per case, an expected OR of 2 (note that there are no studies in the literature that have evaluated the relationship between malnutrition and ESBL-E), an alpha risk of 0.05, and a power of 0.80, for an expected proportion of exposed controls of 0.2 (based on an indicative rate of malnutrition in the hospital population ranging from 20% to 70%), taking into account a matched case-control study design (with a theoretical correlation between case and control of 0.3), the total number of subjects required is 399 (133 cases and 266 controls) for the analysis of the primary outcome measure.

Data management for missing and aberrant data

Missing data management included the use of a data imputation method adapted to the type of missing data, particularly for data that are not 'missing at random'. If it was not possible to manage missing data for certain variables, those variables were not included in the analysis. Our study, which relied on the collection of retrospective data, may have contained numerous aberrant and missing data. To address this issue, we took measures that were specific to the type of variable and the reason for missingness. The management of missing data concerning

exposure criteria was particularly critical due to the potential for classification bias. To deal with this, we developed three models, of which only the first was used to answer the primary research question and the two others were used as sensitivity analysis.

The primary model used in this study was an imputed model based on the multiple imputation method MICE (Multivariate Imputation by Chained Equations). MICE is a powerful technique that can be used to impute missing values for multiple variables, including risk factors and outcomes^{23,24}.

In constructing the MICE model, it was important to account for the collinearity between the outcome and the variables used to construct it. To evaluate this point, two models were constructed: one with imputed values for the outcome, and another with the outcome recalculated based on the imputed variables. The convergence of these two models was then evaluated.

For the sensitivity analysis, we considered missing data for the evaluation of malnutrition in two ways: first, by assuming that all patients with missing data were non-malnourished ("best" model) and second, by assuming that all patients with missing data were malnourished ("worst" model). We analysed these two models exhaustively in Table 2a, which can be found in the Appendix.

Data analysis

Descriptive statistical analysis was employed to summarize the quantitative variables, which were presented as the mean and standard deviation (SD) for normally distributed variables or the median and interquartile range (IQR) for non-normally distributed variables. The comparison of quantitative variables was performed using either a linear model ANOVA or a

Mood's median test. Qualitative variables were described by their count and percentage and compared using a Chi-square test or a Fisher exact test.

To determine the relationship between exposure and disease, a conditional logistic regression has been used to calculate the cOR. The estimates were provided with their 95% Confidence Intervals (CI95%).

For the analysis of secondary outcomes, a multivariate analysis was conducted using a conditional multivariate logistic regression adjusted for different risk factors to obtain aOR and their CI95%. The validity of the model was assessed using correlation matrix and the analysis of linearity, which are presented in Table 3a and Figure 1a in the appendix.

The threshold for statistical significance for descriptive analyses is a p-value <0.05 with an alpha of 5% under the null hypothesis of equality of means or proportions.

All statistical analyses were performed using R studio software (Version 1.4.1103 © 2009-2021 RStudio, PBC).

Ethics

According to current regulations, our research falls outside the scope of the Jardé Law (MR-004) and does not require validation from the Committee for the Protection of Persons before its implementation. Study ethics approval was obtained on 31 December 2021 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

Research Protocol

The research protocol was written according to international STROBE guidelines adapted for case-control studies²⁵. The protocol was approved and validated by the Clinical Research and Innovation Delegation of the CHU GA.

Results

A total of 100,268 samples with Enterobacteriaceae were collected at CHU GA between January 1st, 2010, and December 31st, 2018. A total of 41,295 patients had at least one positive sample (Figure 1). After selecting for inclusion criteria, 61,280 samples were taken from a total of 24,645 patients. Of them, 2,109 patients were positive for ESBL-E and 22,536 were positive for non-producing ESBL-E.

Proportion on ESBL-E changed during years in CHU GA population, it started at 5.3% in 2010, it reached a pic of 10% between 2014-2015 and then stabilized around 7-9%. The most represented bacteria were *E. coli* (63.5%) and *K. pneumoniae* (8.1%).

After case-control matching, the study population consisted of 6,218 patients: 2,099 cases and 4,119 controls. Specifically, 2020 cases were matched with two controls, 79 cases were matched with one control.

In the case-control matched population the proportion of bacteria were different with 70.25% of *E. coli* and 18.91% of *K. pneumoniae*.

Study population characteristics

In total, 53.09% of patients in the study population were female, with a median age in the female population of 77 years [IQR 61-86] and 69 years for males [IQR 58-80] (Table 1).

The patients were hospitalized for a median of 16 days (d) [IQR 8-31], longer in cases than in control (19d with [IQR 9-39] vs 14d with [IQR 8-27], $p < 0.005$). Length of stay prior to infection was also longer in cases than in controls (a median of 4.62 days in case group and 2.49 days in control group, $p < 0.05$).

The percentage of patients with a Charlson comorbidity index ≥ 2 was 59.30% of the population. A more elevated proportion of multimorbid patients was found in case group than in control group (61.46% vs 58.19%, $p < 0.005$). The most common comorbidity was cancer (29.27%), followed by congestive heart failure (20.26%), renal disease (12.12%) and presence of cardiopulmonary disease (11.24%).

Nutritional status

The study population had a mean **height** of 166 cm (SD 9.69), with 24.16% of missing data. No significant difference was found between cases and controls.

Regarding **weight**, the closest measure to the date of sampling had a mean of 68.97 kg (SD 17.91) without any significant difference between cases and controls. Although, 49.22% of the weight data were missing. Of the available data, 36.5% of patients had a $>5\%$ reduction in weight in one month (41.30% missing data), and 28.5% had a weight difference of 10% in the 6 months preceding the positive sampling (35.01% missing data).

The mean **BMI** in the study population was 25.14 kg/m² (SD 7.31) with 60.5% of missing data. Based on available data, 22.5% of the population had a reduced BMI (less than 18.5 kg/m² for those aged 70 and over and less than 21 for younger subjects) without any difference between cases and controls.

The measurement of **albumin**, evaluated in subjects aged ≥ 70 years old (3,487 patients), was found only in 13.4% of patients and 80.0% of them had an albumin level < 35 g/L (threshold for malnutrition criteria), without any difference between cases and controls.

At least one factor on nutritional status was evaluable on 4,583 patients (73.7%).

Analysis of relation between malnutrition and ESBL-E infection

Bivariate analysis

According to MICE model of imputation, the proportion of malnourished patients were respectively 74.96% of cases and 73.54% of controls, with a cOR for malnutrition of 1.10 [CI95% 0.92-1.31] (Table 2).

The analysis of risk factors of ESBL-E infection showed that 49.8% of the population had a history of hospitalization in the 12 months preceding the positive sample, with a significant difference between cases and controls (59.98% in case group vs 44.57% in control group [p<0.005]). Similarly, the use of antibiotics was higher in cases than in controls (15.48% vs 3.23% [p<0.005]). Invasive procedures carried out during the hospital stay were also more often performed in cases than in controls (13.29% vs 5.63% [p<0.005]).

Another known risk factor of ESBL-E infection was a history of colonization with ESBL-producing bacteria in the year preceding the positive sample, and colonization were more frequent in cases than in control (31.66% vs 3.17% [$p < 0.005$]).

Additionally, a more elevated Charlson comorbidity index was related to the risk of ESBL-E infection with a cOR of 1.07 [CI95% 1.04-1.10]. As for the length of stay prior to infection was statistically different between groups but with a cOR of 1 [CI95%1.00-1.00].

Multivariate analysis

After adjusting on risk factors statistically significant on the bivariate analysis (use of antibiotics, previous hospitalization, invasive procedures, previous colonization with ESBL-E, Charlson index) and the length of stay prior to infection, the aOR of malnutrition remain similar and not statistically significant aOR=1.11 [CI95% 0.86-1.43] (Table 2).

The following risk factors of ESBL-E infection remain statistically significant in multivariate analysis (Table 2): invasive procedure (aOR=2.24 [CI95% 1.70-2.96]), previous hospitalisation (aOR=1.76 [CI95% 1.51-2.06]), previous use of antibiotics (aOR=4.49 [CI95% 3.31-6.09]), previous colonisation by ESBL-E (aOR=12.45 [CI95% 8.40-18.45]). Length of stay prior to infection was statistically different between groups but with an aOR very close to 1 [CI95%1.00-1.00]. Charlson comorbidity index, however, didn't represent a risk of ESBL-E infection anymore (aOR= 1.30 [CI95% 0.19-8.89]).

The MICE model was tested both with and without the inclusion of the outcome criteria. However, when the outcome criterion was included in the model, it did not converge due to collinearity with other nutrition criteria included in the model. Therefore, the model without the outcome criteria was ultimately selected.

The sensitivity analysis conducted to assess the impact of the missing data on nutritional status, showed a cOR=1.28 [CI95% 1.15-1.43] for the “best model” and a cOR= 1.06 [CI95% 0.95-1.18] for the “worst model”. In the multivariate analysis, for both models, results of malnutrition as a risk factor of ESBL-E infection were not statistically significant. However, in this last analysis, invasive procedures, previous hospitalisation, previous antibiotics use, ESBL-E colonisation, and length of stay prior to infection were still a significant risk for ESBL-E infection (Table 2a).

Analysis on the sub-population without any identified risk factors

A total of 120 cases and 309 controls were included. At least one malnutrition criterion was evaluated in 317 patients (89 cases and 228 controls). Imputation using the MICE technique did not converge properly, resulting in unreliable results.

Regrettably, also the multivariate logistic regression model applied to this population did not converge adequately, leading to unreliable results.

Discussion

Our study didn't identify malnutrition as a risk factor for ESBL-E infection with an cOR of 1.10 (95% CI 0.92-1.31) calculated with MICE model. However, we found that several risk factors for ESBL-E infection, which have been previously reported in literature, were also statistically significant. Our results showed that undergoing invasive procedures (aOR=2.16), having a history of previous hospitalization (aOR=1.73), previously using of antibiotics (aOR=4.50), and having a previous history of ESBL-E colonization (aOR=13.37) were all associated with increased odds of developing ESBL-E infection. The length of stay prior to infection was also statistically

different between cases and controls with a median of 4.62 days in case group and 2.49 days in control group.

Similar results have been already found in literature. Specifically, pre-existing studies founded elevated OR for previous antibiotic use (OR varied from 1.5 to 8.0) and an augmented risk of ESBL-E infection after invasive procedures (OR varied from 2.4 to 4.3)^{3,4,6,7}. These findings highlight the importance of considering these risk factors in the prevention and management of ESBL-E infections to also reduce the length of the hospitalisation for the patient.

Additionally, we have observed an interesting factor that warrants further investigation: the time to onset of infection was found to be statistically different between the two groups and was longer in the cases group. This finding suggests that a longer period of exposure to the hospital environment, potentially increasing the likelihood of contact with ESBL-E. However, further research is needed to confirm this hypothesis.

To interpret the results of this study, is important to evaluate the characteristics of missing data in our study. We encountered challenges in calculating malnutrition status due to a higher than expected number of missing data on the malnutrition criteria. Specifically, we observed that the percentage of missing data on weight and height measures were 49% and 24%, respectively. One contributing factor to this issue was the need for patients to return to the hospital multiple times or have extended stays to obtain repeated measurements of weight, which was a critical factor for assessing malnutrition status.

Regarding risk factors, there weren't any missing data, except for previous colonisation with ESBL-E (screening is recommended only in specific situations like previous hospitalisation with a colonised patient, hospitalisation in a foreign country and stay in nursing homes). These risk

factors, unlike malnutrition, were exhaustively collected from the patient file because they are part of a standardized and computerized process (entry of procedures for hospital budget, prescription of drugs, admission and discharge dates, previous hospitalizations, and entry of laboratory results). Where data collection was left to healthcare professionals during clinical practice, without standardization or any input check and related to the patient's clinical context, the number of missing or aberrant data increased. These results reinforce the validity of our model and the data collection through PREDIMED warehouse. However, a work on traceability is necessary to enable healthcare professionals to write patient files in a simplified, consistent, and systematic manner, which also helps to avoid data entry errors.

Following the multivariate analysis, we aimed to examine the influence of the identified risk factors on the association between malnutrition and ESBL-E infection. To accomplish this, we conducted a sub-group analysis on the patient population without risk factors. Unfortunately, the matched analysis could not be performed as there were an insufficient number of paired case-control groups available for the conditional logistic regression.

The sensitivity analysis highlighted that the OR for malnutrition were not always significant but remained consistent with each other. One of the models developed in the appendix, the "best" model, also reflects clinical practice of not necessarily searching for malnutrition indicators in patients with a clinical picture that does not suggest malnutrition. Indeed, this model reports a significant cOR=1.28 [CI95% 1.15-1.43]. This further raises questions about the impact of missing data on MICE imputation model if data are not "missing at random". In fact, MICE model allows to improve imputation even with a great number of missing data, but always with the hypothesis on data "missing at random". However, if the proportion of missing data is more than 50%, the results are less reliable^{23,24}.

The limitations of this study included a possible classification bias due to missing data on the malnutrition criterion and the inability to collect all the criteria presented in the HAS recommendations, such as food intake or muscle strength reduction. In addition, some risk factors could not be collected, such as travel in the 12 months prior to the sampling date or the type of patient housing, including living in a nursing home or collective housing. The use of antibiotics in the 6 months prior may be underestimated since we could not take into account antibiotic prescription in the city or in other structures. Similarly, the history of hospitalization in a different structure than CHU GA remains unknown, knowing that about a quarter of readmissions are in a different structure than the index hospital^{26,27}. Moreover, this study remains a monocentric retrospective study with all limitations related.

Conclusion

To our knowledge, our study is the first to specifically investigate the relationship between malnutrition and the occurrence of ESBL-E infections.

The use of the **PREDIMED** data warehouse allowed for extensive search and collection of informatic data on each patient. However, a large proportion of data was missing to estimate nutritional status. In order to fully exploit the data warehouse, **improvement in the traceability** of informatic data is necessary. This requires raising awareness among healthcare professionals about the importance of collecting data correctly to improve clinical practices, as well as simplifying data collection software to make it more user-friendly and less prone to errors in data entry.

The results obtained suggest that further investigations are warranted, with a **prospective study** that allows for systematic collection of all criteria to define the malnutrition status.

THÈSE SOUTENUE PAR : Fabiana CAZZORLA

TITRE :

Study on the relationship between nutritional status and infection with Enterobacteriaceae producing Extended-Spectrum Beta-Lactamases (ESBL-E)

CONCLUSION :

We performed a retrospective matched case-control study aimed to investigate whether there is a correlation between malnutrition and the risk of Extended-spectrum beta-lactamases producing Enterobacteriaceae (ESBL-E). High Authority for Health (HAS) 2019 criteria for malnutrition were used and different risk factors related to infection of ESBL-E were collected through PREDIMED data warehouse. A total of 6,218 patients were included: 2,099 cases (infection with ESBL-E) and 4,119 controls (infection with non-producing ESBL-E).

A complex management of missing data was implemented through MICE (Multiple Imputation by Chained Equation) technique. According to this model, the crude Odds Ratio of malnutrition was 1.10 (95% CI 0.92-1.31). After adjusting on others risk factors found, the adjusted Odds Ratio (aOR) of malnutrition remain similar aOR=1.11 (95% CI 0.87-1.42).

Identified risk factors as invasive procedures (aOR=2.16 [95% CI 1.64-2.86]), previous colonisation with ESBL-E (aOR=13.37 [95% CI 8.46-21.15]), previous hospitalisation (aOR=1.73 [95% CI 1.48-2.03]) and previous antibiotics use (aOR=4.50 [95% CI 3.35-6.05]) were positively correlated to the risk of ESBL-E infection.

To our knowledge, our study is the first to specifically investigate the relationship between malnutrition and the occurrence of E-BLSE infections.

The use of the PREDIMED data warehouse allowed for extensive search and collection of informatic data on each patient. However, a large proportion of data was missing, such as weight and height measurements (49.22% and 24.16% respectively). In order to fully exploit the data warehouse, improvement in the traceability of informatic data is necessary. This requires raising awareness among healthcare professionals about the importance of collecting data correctly to improve clinical practices, as well as simplifying data collection software to make it more user-friendly and less prone to errors in data entry.

The results obtained suggest that further investigations are warranted, with a prospective study that allows for systematic collection of all criteria to define the malnutrition status.

VU ET PERMIS D'IMPRIMER

Grenoble, le : 01/03/2023

LE DOYEN DE LA FACULTÉ DE MÉDECINE



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Par délégation
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Pr Jean Luc Bosson

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Tables and figures

Figure 1: Flowchart of population's selection

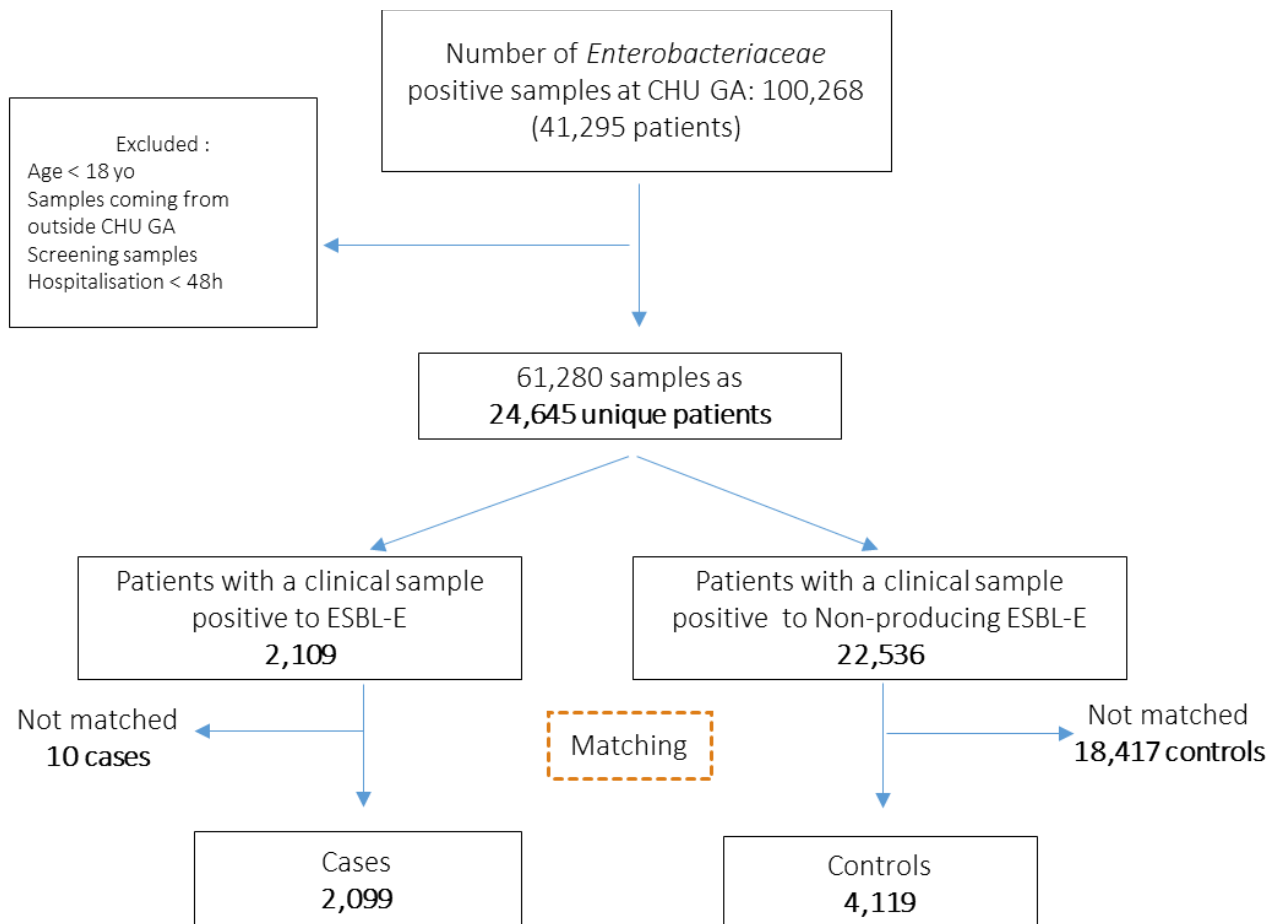


Table 1: Characteristic of the case-control population: demographic details, laboratory details, nutritional status, comorbidities.

	Total (N= 6,218)	Case (N= 2,099)	Control (N= 4,119)	p value
Age (years)				0.64 ¹
Median (IQR)	73.00 (59.00-84.00)	73.00 (59.00-84.00)	73.00 (59.00-84.00)	
Age ≥70 years old				0.91 ²
Number (%)	3,487 (56.1)	1,175 (56.0)	2,312 (56.1)	
Sex, n (%)				0.81 ²
Female	3,301 (53.1)	1,110 (52.9)	2,191 (53.2)	
Male	2,917 (46.9)	989 (47.1)	1,928 (46.8)	
Year of sampling, n (%)				1.00 ²
2010	453 (7.3)	151 (7.2)	302 (7.3)	
2011	550 (8.8)	184 (8.8)	366 (8.9)	
2012	538 (8.7)	180 (8.6)	358 (8.7)	
2013	663 (10.7)	223 (10.6)	440 (10.7)	
2014	908 (14.6)	312 (14.9)	596 (14.5)	
2015	910 (14.6)	309 (14.7)	601 (14.6)	
2016	783 (12.6)	263 (12.5)	520 (12.6)	
2017	717 (11.5)	242 (11.5)	475 (11.5)	
2018	696 (11.2)	235 (11.2)	461 (11.2)	
Type of bacteria, n (%)				1.00 ²
<i>Citrobacter complexe freundii</i>	48 (0.8)	17 (0.8)	31 (0.8)	
<i>Citrobacter koseri</i>	27 (0.4)	9 (0.4)	18 (0.4)	
<i>Enterobacter aerogenes</i>	47 (0.8)	16 (0.8)	31 (0.8)	
<i>Enterobacter complexe cloacae</i>	414 (6.7)	141 (6.7)	273 (6.6)	
<i>Escherichia coli</i>	4,368 (70.2)	1,456 (69.4)	2,912 (70.7)	
<i>Klebsiella oxytoca</i>	58 (0.9)	21 (1.0)	37 (0.9)	

	Total (N= 6,218)	Case (N= 2,099)	Control (N= 4,119)	p value
<i>Klebsiella pneumoniae</i>	1,176 (18.9)	410 (19.5)	766 (18.6)	
<i>Morganella morganii</i>	12 (0.2)	4 (0.2)	8 (0.2)	
<i>Proteus mirabilis</i>	35 (0.6)	12 (0.6)	23 (0.6)	
<i>Proteus spp</i>	7 (0.1)	3 (0.1)	4 (0.1)	
<i>Serratia marcescens</i>	26 (0.4)	10 (0.5)	16 (0.4)	
Length of hospitalisation (days)				< 0.05¹
Median (IQR)	16.00 (8.00-31.00)	19.00 (9.00-39.00)	14.00 (8.00-27.00)	
Time of onset of infection (days)				< 0.05¹
Median (IQR)	3.00 (1.00-10.46)	4.62 (1.00-15.65)	2.49 (1.00-8.71)	
Charlson comorbidity index, n (%)	N= 5,507	N= 1,809	N= 3,698	< 0.05²
1	1,820 (33.0)	519 (28.7)	1,301 (35.2)	
2	399 (7.2)	129 (7.1)	270 (7.3)	
3	1,499 (27.2)	492 (27.2)	1,007 (27.2)	
4	490 (8.9)	194 (10.7)	296 (8.0)	
5	483 (8.8)	174 (9.6)	309 (8.4)	
6	164 (3.0)	66 (3.6)	98 (2.7)	
7	394 (7.2)	132 (7.3)	262 (7.1)	
8	94 (1.7)	41 (2.3)	53 (1.4)	
9	98 (1.8)	30 (1.7)	68 (1.8)	
10	34 (0.6)	20 (1.1)	14 (0.4)	
11	18 (0.3)	7 (0.4)	11 (0.3)	
12	6 (0.1)	2 (0.1)	4 (0.1)	
13	6 (0.1)	2 (0.1)	4 (0.1)	
14	2 (0.0)	1 (0.1)	1 (0.0)	
Albumine (g/L)	N= 3,097	N= 1,195	N= 2,002	< 0.05³
Mean (SD)	28.57 (6.88)	27.99 (6.73)	29.29 (7.00)	

	Total (N= 6,218)	Case (N= 2,099)	Control (N= 4,119)	p value
Previous hospitalisations				< 0.05²
Number (%)	3,095 (49.8)	1,259 (60.0)	1,836 (44.6)	
Previous use of antibiotics				< 0.05²
Number (%)	458 (7.4)	325 (15.5)	133 (3.2)	
Invasive procedures				< 0.05²
Number (%)	511 (8.2)	279 (13.3)	232 (5.6)	
Previous ESBL-E colonisation	N= 1,518	N= 698	N= 820	< 0.05²
Number (%)	247 (16.3)	221 (31.7)	26 (3.2)	
Height (cm)	N= 4,716	N= 1,652	N= 3,064	0.85 ³
Mean (SD)	166.11 (9.69)	166.07 (9.72)	166.13 (9.68)	
Weight (Kg)	N= 3,157	N= 1,087	N= 2,070	0.35 ³
Mean (SD)	68.97 (17.91)	69.38 (18.18)	68.75 (17.77)	
BMI (kg/m²)	N= 2,386	N= 852	N= 1,534	0.29 ³
Mean (SD)	25.14 (7.31)	25.35 (7.44)	25.02 (7.23)	
Malnutrition based on albumin level	N= 3,097	N= 1,195	N= 2,002	0.80 ²
Number (%)	373 (80.0)	218 (80.4)	155 (79.5)	
Malnutrition based on BMI	N= 2,386	N= 852	N= 1,534	0.83 ²
Number (%)	566 (23.7)	200 (23.5)	366 (23.9)	
Malnutrition based on 1 month weight difference	N= 3,650	N= 1,236	N= 2,414	0.67 ²
Number (%)	1,332 (36.5)	457 (37.0)	875 (36.2)	
Malnutrition based on 6 months weight difference	N= 4,041	N= 1,367	N= 2,674	0.66 ²

	Total (N= 6,218)	Case (N= 2,099)	Control (N= 4,119)	p value
Number (%)	1,150 (28.5)	395 (28.9)	755 (28.2)	
Estimation of nutritional status				< 0.05²
Number (%)	4,583 (73.7)	1,610 (76.7)	2,973 (72.2)	

BMI = Body mass Index

ESBL-E = Extended spectrum Beta Lactamases *Enterobacteriaceae*

1. *Mood's median test*
2. *Pearson's Chi-squared test*
3. *Linear Model ANOVA*

Table 2: Conditional logistic regression, bi-variate and multi-variate analysis of factors associated with ESBL-E infection.

	cOR (CI95%)	P value	aOR (CI95%)	P value
Length of stay prior to infection	1.00 (1.00-1.00)	<0.05	1.00 (1.00-1.00)	0.01
Invasive procedures	2.68 (2.21-3.24)	<0.05	2.24 (1.70-2.96)	<0.05
Previous hospitalisation	1.88 (1.68-2.09)	<0.05	1.76 (1.51-2.06)	<0.05
Previous antibiotics use	5.66 (4.54-7.06)	<0.05	4.49 (3.31-6.09)	<0.05
ESBL-E colonisation	19.25 (8.43-43.95)	<0.05	12.45 (8.40-18.45)	<0.05
Charlson comorbidity index	1.07 (1.04-1.10)	<0.05	1.30 (0.19-8.89)	0.79
Malnutrition	1.10 (0.92-1.31)	0.30	1.11 (0.86-1.43)	0.41

ESBL-E = Extended spectrum Beta Lactamases *Enterobacteriaceae*

Appendix

Table 1a: Acceptability time frame for each studied variable

Variable	Population	Time frame	Acceptability time frame
Weight	All	1. Date of sampling 2. One month before sampling 3. Six months before sampling	10 days before or after the date of sampling
Height	All	Date of sampling	Any date after 18th birthday of the patient
BMI	All	Date of sampling	10 days before or after the date of sampling
Albumin level	More than 70 yo	Date of sampling	10 days before or after the date of sampling
Previous Hospitalisation	All	During 12 months before date of sampling	-
Previous antibiotics use	All	During 6 months before date of sampling	-
Urinary catheter	All	During actual hospitalisation and before the date of sampling	-
Arterial or venous catheter	All	During actual hospitalisation and before the date of sampling	-
Artificial ventilation	All	During actual hospitalisation and before the date of sampling	-

BMI = Body mass Index

Table 2a: Sensitivity analysis: multivariate logistic regression

In the "best" model, a total of 2,296 patients were malnourished and 3,922 patients were not. The cOR was significant at 1.28 (95% CI 1.15-1.43).

In the "worst" model, 3,931 patients were classified as malnourished and 2,287 were not. The cOR was then not significant (cOR=1.06, 95% CI 0.95-1.18).

Multivariate analysis results, calculated on a total population of 1,342 patients, are presented in table below.

	"Best model"¹ aOR (CI95%)	P value	"Worst model"² aOR (CI95%)	P value
Length of stay prior to infection	1.04 (1.02-1.06)	<0.05	1.03 (1.01-1.06)	<0.05
Invasive procedures	1.56 (0.84-2.90)	0.16	1.55 (0.83-2.89)	0.17
Previous hospitalisation	1.81 (1.11-2.96)	<0.05	1.87 (1.15-3.04)	<0.05
Previous antibiotics use	2.55 (1.19-5.46)	<0.05	2.55 (1.19-5.47)	<0.05
ESBL-E colonisation	18.78 (7.61-46.34)	<0.05	18.76 (7.63-46.09)	<0.05
Charlson index	1.00 (0.90-1.11)	0.96	1.00 (0.90-1.11)	1.00
Malnutrition	1.13 (0.71-1.80)	0.60	0.85 (0.55-1.33)	0.48

ESBL-E = Extended spectrum Beta Lactamases *Enterobacteriaceae*

¹ missing data on malnutrition were considered as not malnourished

² missing data on malnutrition were considered as malnourished

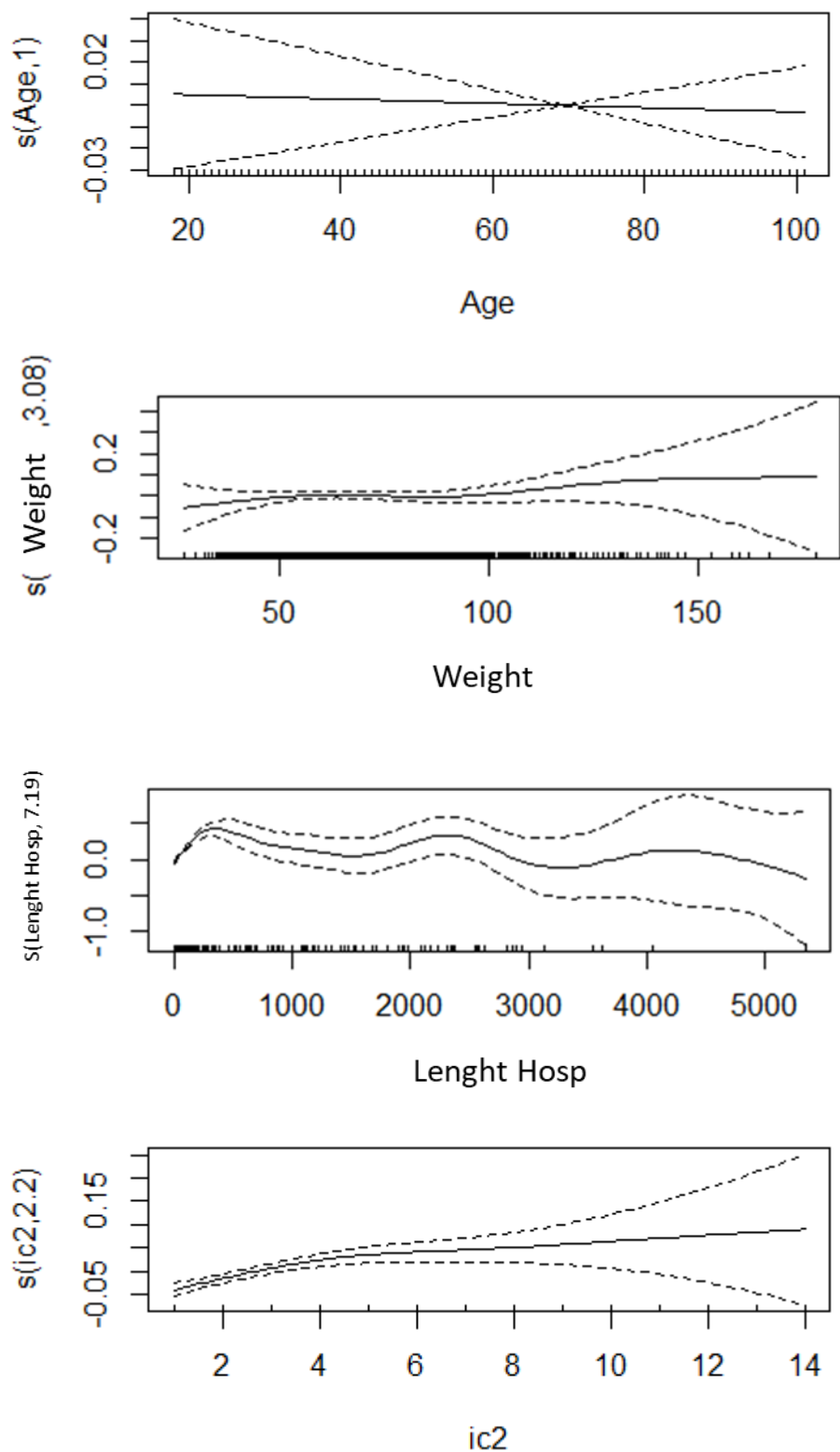
Table 3a: Correlation matrix among studied variables

	1 month weight	6 months weight	weight malnutrition	BMI	BMI malnutrition	albumin	albumin malnutrition	invasive procedures	previous hospitalisation	Previous antibiotic use	ESBL-E colonisation	Charlson index
1 month weight	1	0.53	0.87	-0.03	0.04	0.06	-0.09	-0.01	0	0.03	-0.01	0
6 months weight	0.53	1	0.75	-0.06	0.05	0.03	-0.04	-0.03	-0.02	0.02	-0.02	-0.02
weight malnutrition	0.87	0.75	1	-0.05	0.05	0.05	-0.07	-0.02	-0.01	0	-0.02	-0.01
BMI	-0.03	-0.06	-0.05	1	-0.61	0.06	-0.1	-0.02	-0.04	-0.03	0.02	-0.02
BMI malnutrition	0.04	0.05	0.05	-0.61	1	-0.03	0.01	-0.01	0.01	0.01	-0.02	-0.01
albumin	0.06	0.03	0.05	0.06	-0.03	1	-0.72	-0.24	-0.01	-0.1	0.08	-0.19
albumin malnutrition	-0.09	-0.04	-0.07	-0.1	0.01	-0.72	1	0.12	0.08	0.05	0	0.12
invasive procedures	-0.01	-0.03	-0.02	-0.02	-0.01	-0.24	0.12	1	-0.02	0.21	0.07	0.09
Previous hospitalisation	0	-0.02	-0.01	-0.04	0.01	-0.01	0.08	-0.02	1	0.17	0.05	0.16
Previous antibiotic use	0.03	0.02	0	-0.03	0.01	-0.1	0.05	0.21	0.17	1	0.08	0.08
ESBL-E colonisation	-0.01	-0.02	-0.02	0.02	-0.02	0.08	0	0.07	0.05	0.08	1	-0.01
Charlson index	0	-0.02	-0.01	-0.02	-0.01	-0.19	0.12	0.09	0.16	0.08	-0.01	1

BMI = Body mass Index

ESBL-E = Extended spectrum Beta Lactamases *Enterobacteriaceae*

Figure 1a: Plots to evaluate linearity of variables



Scatter plot allowed to estimate the linearity of some important variables. Age was linear with a bigger proportion of patients among 60 and 80 years old; estimation of weight was also linear; Length of Hospitalisation (Length Hosp) was more fluctuant and not linear especially on longer stays; Charlson comorbidity index (ic2) was linear especially for smaller values.

*L*e serment d'Hippocrate

Texte revu par l'Ordre des médecins en 2012

“ Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité. Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque. ”