Not-for-profit observational study to evaluate the quality and safety of care in *outliers* hospitalized with medical diseases - Study Protocol of Safety Issues and SurvIval For Medical Outliers (SISIFO study)

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ABSTRACT

The progressive cutting of hospital beds in some health systems, together with the increased needs related to the aging population, has led to the phenomenon of patients hospitalized outside the appropriate ward (*outliers*). This is particularly relevant in the context of Internal Medicine. Despite its relevance in daily clinical practice, available evidence for the potential impact of this phenomenon is limited. The aim of this study is to evaluate the effects of this situation on patients' outcomes and possibly identify organizational and managerial aspects related to the presence of outliers. The multicenter, observational, prospective Study Protocol of Safety Issues and SurvIval For Medical Outliers (SISIFO) was promoted by the Italian Federation of Associations of Hospital Doctors on Internal Medicine (FADOI). The primary study endpoint is the evaluation of in-hospital mortality in outliers *versus* controls. A sample size of 2400 patients has been estimated by assuming a mortality rate of 12% and 8% in outliers and controls, respectively. By virtue of the multicentric dimension, the expected number of patients, and the controlled design, the FADOI-SISIFO study might provide interesting and useful findings to better manage the phenomenon of outliers.

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*See Appendix I for the list of sites and Investigators

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Introduction

In Italy, the progressive cutting of hospital beds (45,000 from 2000 to 2009), not preceded by an accurate estimate of health needs in relation to the aging population, nor associated with a strengthening of out-of-hospital services, but rather combined with a hospitalized-centric conception of health by citizens and an increase in difficult hospital discharges due to social and health fragility, has led in recent years, especially in winter, to unavailability of beds, mostly in the medical area, resulting in hospitalization *outside the clinically appropriate ward*.

Patient hospitalized *outside the clinically appropriate ward*, also called in the international literature *outlier*, *out-lying hospital in-patient*, *overflow*, *sleep-out* or *boarder*,[1-3] is a patient who, for lack of free beds in the clinically appropriate ward, is sent by the Emergency Room to another ward with beds availability.

In this case, the medical management is in charge of the appropriate clinical ward and nursing and support assistance of the hosting ward.

The hospitalizations *outside the ward* are typical of countries with a public health system; they amount to about 7-8% and assume dramatic characteristics in size and sustainability.

Available evidence about this phenomenon is few and of low methodological quality. Existing studies report: i) a trend toward a longer hospitalization for the *outliers*;[1,4-6] ii) an inconstant increase in mortality and 30-day re-admission rate;[4,5] iii) worse outcomes for patients with stroke, burns, asthma and gastrointestinal bleeding not admitted to clinically appropriate wards;[7-10] iv) more calls to the intra-hospital emergency system for the *outliers*;[11] v) less competence of nurses in the management of trauma patients outside the appropriate ward;[12] vi) less satisfaction of patients and operators with mutual concerns about the quality and safety of care;[2,3] vii) reduction of the phenomenon and its related mortality by organizational interventions such as *doctor of the week*, facilitation of hospital discharges or *quick and sick* ward;[13,14] viii) increased vulnerability to risks for the *outliers*;[15] ix) additional workload for caring physicians also for the movement between the wards;[16] x) delay in elective surgeries.[17]

In summary, the literature provides us with a series of insights about risks and outcomes for the outliers. However, the size and statistical power of existing studies are insufficient to definitively demonstrate that outliers' status increase mortality (in-hospital and/or at 30 or 90 days) and decrease quality and safety of care, as it is generally perceived.

To answer these research questions, the Italian Italian Federation of Associations of Hospital Doctors on Internal Medicine (FADOI) promoted the Study Protocol of Safety Issues and SurvIval For Medical Outliers (SISIFO), whose protocol is the object of the present work.

The SISIFO study aims to bring closer the constant effort that the Internal Medicine Units (IMUs) or similar perform every day in reabsorbing the admissions *outside the ward* but finding new ones the day after, as the mythical effort of Sisyphus condemned for eternity to push a boulder from the base to the top of a mountain.

Aim of the study

On such premises, the primary endpoint of the SISIFO study is the evaluation of the in-hospital mortality in *outliers* (*cases*) compared to patients that are hospitalized *ab initio* in the clinically appropriate ward (*controls*).

Among the secondary endpoints of the study, there are many comparisons between cases and controls, including: i) assessment of adverse events; ii) mortality rate at 30 and 90 days; iii) length of hospital stay; iv) the number of 30-day and 90-day re-admissions.

Materials and Methods

The SISIFO study has been designed as a multicenter, prospective, not-for-profit observational study (NCT03651414). It involves 36 Internal Medicine Units or similar in Italy. This large number of sites located throughout the country might allow achieving interesting indications in terms of comparison between the different wards/regions.

The study started in October 2018 and closed prematurely due to the COVID-19 pandemic. Despite this, more than 2000 patients have been enrolled.

As a general rule, each site was requested to recruit patients according to this scheme: 40 consecutive patients hospitalized for any cause that spend at least one night *outside the ward* (*outliers*) and 30 consecutive patients immediately hospitalized in the clinically appropriate ward (*controls*).

This study was the project work of the II level University Master '*Hospitalist. The governance of complexity in Hospital Internal Medicine*' held at Genoa University in 2018-2019. For this reason, 8 sites that did not have *outliers* recruited only consecutive controls.

In details, the inclusion criteria of *outliers* were: i) age ≥18 years; ii) signature of informed consent; iii) patients coming from Emergency Room; iv) patients hospitalized in IMUs or similar (not day-hospital) but patients spending at least one night in another ward for lack of available beds; v) consecutive cases. The inclusion criteria of *controls* were: i) age ≥18 years; ii) signature of informed consent; iii) patients coming from Emergency Room; iv) patients hospitalized *ab initio* in IMUs or similar for at least one night; v) consecutive cases.

The exclusion criteria of both groups were: i) age <18 years; ii) patients hospitalized in IMUs or similar coming from other wards or directly from home; iii) consent denied.

Patient data were collected by an electronic Case Report Form (eCRF). To ensure patients' privacy, they were identified only by a progressive code number for each site participating in the study. The protection of individuals was guaranteed as recommended in the Oviedo Convention and the Helsinki Declaration. All patients were asked to sign an Informed Consent and a Consent to the processing of personal data.

Among the data collected there were: i) general information about the site; ii) general information about the patient (gender, age, *etc.*); iii) medical history and drugs; iv) vital signs and modified early warning score; v) examinations done during hospitalization; vi) outcome during hospitalization; vii) 30-day and 90-

day follow up for survival and re-admission to hospital. Approval for the study was obtained from the Ethics Committees of all participating centers.

A sample size of 1200 patients per group (*outliers* and *controls*) was estimated by assuming an in-hospital mortality rate of 8% in the group of patients admitted from the first day in the clinically appropriate ward and 12% in the group of *outliers*, with an α error of 0.05 and a statistical power (error 1-β) of 90%.

The statistical analysis of the collected data will be developed through two distinct phases: i) descriptive analysis; ii) inferential analysis.

The purpose of the first phase will be to provide a synthetic representation of the sample and its main characteristics. In this phase, aggregations may be conducted in order to understand the prevalence of certain phenomena (mortality and prevalence of adverse events, *etc*.) both as a point datum (relating to the site) and as a regional datum (aggregation of several sites of the same geographical origin) and, finally, as a national datum. On an inferential basis, a multivariable analysis will be conducted to understand which organizational and managerial factors affect the presence of *outliers* and adverse events. Multivariable analyses will be conducted in accordance with the rule of thumb, which states that the rate between the events to be analyzed and the variables considered in the predictive model is approximately not lower than 10.

All categorical variables measured in this study will be expressed as an absolute number and percentage. Continuous variables will be expressed as mean and standard deviation or median and interquartile range, depending on the normal or abnormal data distribution.

Differences will be analyzed by chi-squared test, t-tests for unpaired data, or Mann-Whitney U test, depending on the nature of the variable. The difference between the study groups for the primary endpoint (in-hospital mortality) will be expressed in terms of incidence rate ratio, with the relevant 95% confidence intervals. Differences with a $P<0.05$ will be considered statistically significant.

Discussion

Despite its relevance in daily clinical practice, that of *outliers* is a phenomenon still little studied systematically, as can be seen from the review of the literature presented above.

The purpose of our study is primarily to fill, with a suitable and multicentric sample, an information gap concerning the impact in terms of mortality and adverse events of patients hospitalized *outside the clinically appropriate ward*. After that, collected data might help to identify the organizational and managerial risk factors that can be related to the presence of *outliers*, in order identify possible actions for mitigation of the phenomenon and/or improvement of its outcomes.

Conclusions

By virtue of the multicentric dimension, the expected number of patients, and the controlled design, the FADOI-SISIFO study might provide interesting and useful findings to better manage the phenomenon of outliers.

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*APPENDIX I

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