"General Deterioration": A Diagnosis that is a Marker for Risk of Mortality upon Re-Admission

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ABSTRACT: **Background:** Predicting mortality is important in treatment planning and professional duty towards patients and their families.

Objectives: To evaluate the predictive value regarding patients' survival once the diagnosis of "general deterioration" replaces an ICD-9 diagnosis upon re-admission.

Methods: In this retrospective cohort case-control study, we screened the records of patients re-admitted at least three times during the past 2 years. For each patient's death during the third hospitalization, we matched (for age and gender) a patient who survived the third hospitalization. We evaluated 14 parameters potentially accountable for increased risk of mortality, e.g., length of stay at each admission, interval to re-admission, etc. We applied a multifactorial analysis using logistic regression to predict the risk of mortality during the third hospitalization as potentially affected by the aforementioned parameters.

Results: The study included 81 study patients and 81 controls. Of the 14 parameters potentially explaining an increased risk of mortality during the third hospitalization, several were found to be statistically significant. The most significant was the diagnostic switch from a specific ICD-9 diagnosis on first admission to the non-specific diagnosis of "general deterioration" at the second hospitalization. In such cases, the risk of death during the third hospitalization was increased by 5300% (odds ratio = 54, $P = 0.008$). The increased risk of mortality was not restricted to patients with malignancy as their background diagnosis.

Conclusions: At re-admission a switch from disease-specific diagnosis to the obscure diagnosis "general deterioration" increases the subsequent risk of mortality.

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KEY WORDS: diagnosis, general deterioration, mortality, internal medicine

Establishing and communicating an accurate prognosis to patients and their families is a major professional duty of physicians [1], becoming especially challenging in the case of re-admitted patients. Prognostic evaluation is based not only on measurable data (e.g., laboratory values and imaging findings) but also relies heavily on the cumulative clinical appreciation of physicians during the patient's re-hospitalizations. This accumulating appreciation is influenced by the "working diagnosis" of each admitting physician. In contrast to a large number of publications that correlate measurable objective data (e.g., serum albumin [2]) of rehospitalized patients and their prognosis, or studies evaluating specific cohorts of patients (e.g., with chronic obstructive pulmonary disease [3]), the literature has scarce information on the extent to which clinical judgment affects the prognosis.

The current study was meant to confirm our clinical impression that re-admitted patients whose admission diagnosis was switched from a disease-specific ICD-9 encoded diagnosis to the obscure spectrum of diagnoses known as "general/functional deterioration" have a markedly ominous prognosis. It should be further stated that "general deterioration," although commonly documented by internists, at least in Israel, is not encoded by the ICD-9. Nevertheless, Ben-Yehuda et al. [5] recently found that the diagnosis of "general deterioration" increases the risk for medication error [5].

PATIENTS AND METHODS

In a retrospective cohort case-control study we evaluated the records of all patients re-admitted at least three times to our ward during the past 2 years. All data were collected after study approval by the institutional ethics committee. For each patient who died during the third hospitalization, we matched (for age and gender) a patient who survived the third hospitalization. A total of 162 patients were included in the study: 81 study patients and 81 controls.

Although computerized, all patients' records were manually screened since many admission diagnoses were not encoded according to the ICD-9. Admission diagnosis frequencies across hospitalizations were compared.

Statistical analysis was performed by SAS for Windows version 9.2. The following 14 parameters, potentially accountable for increased risk of mortality during the third hospitalization, were analyzed by bivariate analysis:

- Length of stay during the first hospitalization
- Length of stay during the second hospitalization

- Length of stay during the third hospitalization
- Interval between first and second hospitalization
- Interval between second and third hospitalization
- Switch of "Admission diagnosis" between first and second hospitalizations
- Switch of "Admission diagnosis" between second and third hospitalizations
- Malignancy as the primary background diagnosis
- Cardiovascular disease as the primary background diagnosis
- First admission diagnosis switched to "general deterioration" upon re-admission
- Second admission diagnosis switched to "general deterioration" upon re-admission
- First admission diagnosis is "general deterioration"
- Second admission diagnosis is "general deterioration"
- Third admission diagnosis is "general deterioration."

Continuous parameters were compared using the Wilcoxon-signed rank test whereas categorical parameters were compared using the McNemar test. A multivariate conditional logistic regression model was applied to the data to predict the probability of mortality in the third hospitalization as a function of the explanatory variables that were found to have a statistical significance of at least 0.07 in the bivariate analysis.

RESULTS

A total of 162 patients were included in the study: 81 study patients and 81 controls. Each group included 50.62% females and the mean age for both groups was 78.7 years, which is similar to the mean age of the patient population in our department.

Since there was a myriad of admission diagnoses, some were collected into groups enabling statistical analysis, e.g., cardiac diagnoses such as Acute Coronary Syndrome and Congestive Heart Failure Exacerbation were collectively termed MACE (Major Cardiovascular Events).

Shift of diagnoses between admissions is presented in Table 1. The most common diagnosis during the first hospitalization in the study group was dyspnea, whereas the most common diagnoses during the first hospitalization in the control group were (with equal prevalence) dyspnea and MACE. The most common diagnosis during the second hospitalization for the study group was "general deterioration" and for the control group (still) dyspnea. The most common diagnoses during the third hospitalization in the study group were (with equal prevalence) "general deterioration" and fever, while the most common diagnosis during the third hospitalization in the control group was (still) dyspnea.

In order to identify important factors from the predefined list of parameters we conducted a bivariate analysis [Table 2]. The parameters shown to have a statistically significant effect on mortality during the third hospitalization are: length of stay during the third hospitalization ($P = 0.0008$), the interval between second and third hospitalization ($P = 0.003$), switched admission diagnosis between first and second hospitalization ($P = 0.001$), malignancy as the primary background diagnosis ($P = 0.0016$), a primary background diagnosis not related to the cardiovascular system ($P = 0.0018$), and general deterioration as the second or third re-admission diagnosis ($P = 0.0005$ and $P = 0.03$ respectively).

Table 3 shows a regression analysis by both maximum likelihood estimates (MLE) and odds ratio including nine explanatory variables. Table 4 shows the result of a parsimonious model, performed to identify the most important factors from the nine explanatory variables, by applying the model selection method as backward elimination.

Table 1. The five most prevalent diagnoses in the first, second and third hospitalization, for both study groups

Admission diagnosis (descending order of frequency)	Study group (died during third hospitalization)	Control group (alive through third hospitalization)
First hospitalization		
1	Dyspnea	Dyspnea, MACE
2	Syncope, Pain control	Acute GI complaints*
3	MACE, Fever**	Syncope, Pain control
4	Anemia	Fever**
5	Pneumonia, General deterioration, Acute GI complaints*, Elective procedure##	Renal/Urinary complaints#
Second hospitalization		
1	General deterioration	Dyspnea
2	Dyspnea	Acute GI complaints*
3	Renal/Urinary complaints#	MACE
4	Fever**	Syncope, Pain control, Fever**
5	Anemia, MACE, Pneumonia	Elective procedure##
Third hospitalization		
1	Fever**, General deterioration	Dyspnea
2	Dyspnea	Fever**
3	Pneumonia	MACE, Syncope, Pain control
4	MACE	General deterioration, Acute GI complaints*
5	Anemia, Acute GI complaints*	Neutropenia/Febrile neutropenia

*Our ward is affiliated to the gastroenterology wing, hence there are more GI patients compared to the patient population of the whole medical center

**The diagnosis of "fever" includes both febrile illness with suspected focal infection and patients with "fever for investigation"

#Other than urinary tract infection

##Admission for an elective procedure (e.g., colonoscopy, percutaneous cardiac intervention, etc.)

MACE = major cardiovascular events, GI = gastrointestinal

MACE = major adverse cardiac events

Table 2. Comparison of two groups by bivariate analysis

	Study group (N=81)	Control group (N=81)	*P* value
Length of stay during the first hospitalization	6.48 (6.47)	6.49 (5.71)	0.81*
Length of stay during the second hospitalization	5.59 (4.53)	5.56 (5.75)	0.24*
Length of stay during the third hospitalization	10.43 (9.81)	6.36 (6.22)	0.0008*
Interval between first and second hospitalization	26.5 (21)	33.3 (24.8)	0.06*
Interval between second and third hospitalization	20.5 (16)	32.6 (25.6)	0.003*
Switch of admission diagnosis between first and second hospitalizations	74%	48%	0.001**
Switch of admission diagnosis between second and third hospitalizations	77.8%	64.2%	0.07**
Malignancy as primary background diagnosis	40.7%	16%	0.0016**
Cardiovascular disease as primary background diagnosis	24.7%	48.1%	0.0018**
First admission diagnosis switched to "general deterioration" upon re-admission	17%	0%	NA
Second admission diagnosis switched to "general deterioration" upon re-admission	14.8%	7.4%	0.13**
First admission diagnosis is "general deterioration"	6.17%	2.5%	0.26**
Second admission diagnosis is "general deterioration"	18.5%	1.2%	0.0005**
Third admission diagnosis is "general deterioration"	21%	8.6%	0.03**

*Wilcoxon signed-rank sum test

**McNemar test

A multivariate conditional logistic regression model was applied to the data to predict the probability of mortality during the third hospitalization as a function of the explanatory variables that had a statistical significant level of at least 0.07 in the bivariate analysis.

Table 3. Analysis of maximum likelihood estimates (MLE) and odds ratios (OR) of the full conditional logistic regression to predict mortality in the third hospitalization

	MLE	OR	*P* value
Length of stay during the third hospitalization	0.0291	1.030	0.4037
Time interval (days) between first and second hospitalization	-0.0185	0.982	0.1062
Time interval (days) between second and third hospitalization	-0.0478	0.953	0.0018
Unchanged admission diagnosis between first and second hospitalization	-0.8595	0.423	0.0888
Unchanged admission diagnosis between second and third hospitalization	-1.4643	0.231	0.0167
First admission diagnosis switched to "general deterioration" upon re-admission	3.6766	39.512	0.0113
Second admission diagnosis switched to "general deterioration" upon re-admission	0.4274	1.533	0.5485
Cardiovascular disease as primary background diagnosis	0.5619	1.754	0.4194
Malignancy as primary background diagnosis (%)	2.2448	9.438	0.0045

The important predictors for increased mortality during the third hospitalization are: a switch of the first hospitalization diagnosis to that of "general deterioration" during the second admission (OR = 54.3, $P = 0.008$) and malignancy as the primary background diagnosis (OR = 6.65, $P = 0.0007$).

OR = odds ratio

Table 4. Analysis of maximum likelihood estimates (MLE) and odds ratios of the parsimonious model to predict mortality in the third hospitalization

	MLE	OR	*P* value
Time interval (days) between second and third hospitalization	-0.0444	0.957	0.0003
Unchanged admission diagnosis between second and third hospitalization	-1.2908	0.275	0.0097
First admission diagnosis switched to "general deterioration" upon re-admission	3.9947	54.312	0.0080
Malignancy as primary background diagnosis	1.8953	6.654	0.0007

The important predictors for decreased mortality during the third hospitalization are: prolonged interval (days) between the second and third hospitalization (OR = 0.96, $P = 0.0003$) and unchanged admission diagnosis between the second and third hospitalization (OR = 0.28, $P = 0.0097$).

DISCUSSION

The results of the present study might not come as a surprise to any experienced internist/hospitalist; however, the magnitude of the extent to which the odds ratio of mortality is increased is dramatic.

The relationship of the "General Deterioration" diagnosis to mortality is not straightforward with regard to cause or effect: does the obscure diagnosis of "general deterioration" arise from the admitting physician's appreciation that the patient carries a poor prognosis? At least according to our short residents' survey, this is not the case. Or could it be that the obscure diagnosis lessens the ward physician's attention to the patient later on during his/her hospitalization? The current study cannot answer this question. A potential association is suggested by Ben-Yehuda and co-authors [5]: in their study of patients with medication errors, a diagnosis of "general deterioration" as the main diagnosis upon admission was more common than among controls – 20 (14.6%) vs. 8 (5.8%), $P = 0.017$; while cardiovascular diagnoses were less common – 31 (22.6%) vs. 51 (37.2%), $P = 0.008$.

Our study has two major limitations: the small cohort and the fact that our findings could not be directly applied to hospitals in which there is strict adherence to ICD-9 diagnoses.

CONCLUSIONS

A shift from an ICD coded diagnosis to the relatively obscure diagnosis of "General Deterioration" upon re-admission to the internal ward predicts an extremely increased risk of death. Accordingly, physicians should decide whether they intend to continue using such obscure non-ICD encoded diagnoses. In the event of continued use, one must consider their impact on prognosis when contemplating patients' diagnostic and treatment plans. Such awareness is an inseparable

part of our professional obligations towards our patients and their families.

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Capsule

Topographic diversity of fungal and bacterial communities in human skin

Traditional culture-based methods have incompletely defined the microbial landscape of common recalcitrant human fungal skin diseases, including athlete's foot and toenail infections. Skin protects humans from invasion by pathogenic microorganisms and provides a home for diverse commensal microbiota. Bacterial genomic sequence data have generated novel hypotheses about species and community structures underlying human disorders. However, microbial diversity is not limited to bacteria; microorganisms such as fungi also have major roles in microbial community stability, human health and disease. Genomic methodologies to identify fungal species and communities have been limited compared with those that are available for bacteria. Fungal evolution can be reconstructed with phylogenetic markers, including ribosomal RNA gene regions and other highly conserved genes. Findley et al. sequenced and analyzed fungal communities of 14 skin sites in 10 healthy adults. Eleven core-body and arm sites were dominated by fungi of the genus Malassezia, with only species-level classifications revealing fungal community composition differences between sites. By contrast, three foot sites – plantar heel, toenail and toe web – showed high fungal diversity. Concurrent analysis of bacterial and fungal communities demonstrated that physiologic attributes and topography of skin differentially shape these two microbial communities. These results provide a framework for future investigation of the contribution of interactions between pathogenic and commensal fungal and bacterial communities to the maintenance of human health and to disease pathogenesis.

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Eitan Israeli

Capsule

Severe malaria is associated with parasite binding to endothelial protein C receptor

Sequestration of *Plasmodium falciparum*-infected erythrocytes in host blood vessels is a key triggering event in the pathogenesis of severe childhood malaria, which is responsible for about one million deaths every year. Sequestration is mediated by specific interactions between members of the *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) family and receptors on the endothelial lining. Severe childhood malaria is associated with expression of specific PfEMP1 subtypes containing domain cassettes (DCs) 8 and 13, but the endothelial receptor for parasites expressing these proteins was unknown. Turner et al. identified endothelial protein C receptor (EPCR), which mediates the cytoprotective effects of activated protein C, as the endothelial receptor for DC8 and DC13 PfEMP1. The authors show that EPCR binding is mediated through the amino-terminal cysteine-rich interdomain region (CIDRα1) of DC8 and group A PfEMP1 subfamilies, and that CIDRα1 interferes with protein C binding to EPCR. This PfEMP1 adhesive property links *P. falciparum* cytoadhesion to a host receptor involved in anticoagulation and endothelial cytoprotective pathways, and has implications for understanding malaria pathology and the development of new malaria interventions.

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Eitan Israeli

"Every increased possession loads us with new weariness"

John Ruskin (1819-1900), leading English art critic of the Victorian era, also an art patron, draughtsman, watercolorist, a prominent social thinker and philanthropist