Intensive Care Med (2021) 47:594–597
https://doi.org/10.1007/s00134-021-06420-3

EDITORIAL

Yentl syndrome and the ICU

Julie Helms[1,2*], Audrey De Jong[3] and Sharon Einav[4]

Bayesian statistics interpret data based on prior knowledge (or likelihood) and assume that the individual risk for an event reflects that of the population as a whole. In other words, the probability that an event will occur is based on prior knowledge of conditions that might be related to the event (Supplementary Fig. 1). Bayesian statistics are most correct when based on pre-existing assumptions that have been validated time and time again. They are useful for laboratory testing where the norms are well known. They are also useful for studying heart disease in women as thirty years of research have established that in relation to acute heart syndrome, women and men do indeed differ (the Yentl syndrome). So, if the risk of missing a myocardial infarction is related to the female sex, Bayes' theorem will assess the risk of a missed myocardial infarction for an individual while taking into consideration that they are female rather than male.

However, contrary to early assumptions focusing on inequality alone, it has turned out that the reasons for male–female differences in heart disease are diverse. Heart disease manifests differently in women and men [1–4], there are specific challenges to achieving adherence to treatment and recommendations in women [5, 6], there was insufficient research on the effects of drugs and intervention on women [7–9] and more. And yes, at times, inequalities in care have also been discovered [6, 7].

The proportion of male admissions to intensive care is consistently higher than that of males in the population in general and in the elderly population specifically. In their nationwide retrospective study performed over 5 years on 450,948 adults in Switzerland, with 17.3% admissions to intensive care unit (ICU), Todorov et al. [10] attempt to elicit the reasons for this. Using two large databases, the authors sought gender differences in the provision of care to critically ill patients with cardiological or neurovascular diseases. They found that women were less likely to be admitted to an ICU than men despite being more severely ill, in particular younger women aged less than 45 years. Also, per each unit of increase in SAPS II, the odds of death were significantly higher among women than among men.

We salute the authors for their effort to adjust for the available variables in their analysis, as gender is, in general, a confounder but not when it is the focus of the analysis, like in the paper of Todorov et al. In addition, although they chose a Bayesian approach for analyzing the probability of ICU admission, analysis was conducted using non-informative priors, thus taking into consideration that prior data on differential treatment for men and women in relation to ICU admission is lacking. This improves the likelihood of reaching data-driven rather than bias-driven results. Sensitivity analysis to confirm the assumption that the non-informative priors have no influence on the results because of the size of the dataset, for example a frequentist model similar to the one performed on the secondary objective of death, was not performed even if it would likely have yielded similar results. However, concluding from the data presented that women may have less access to intensive care requires a (great) leap of faith. As stated by Jose Saramago: "Not everything is as it seems, and not everything that seems is. Between being and seeming there is always a point of agreement as if being and seeming were two inclined planes that converge and become one". Much more data is required to elicit the reasons for the findings highlighted by the authors before the flag of inequality is raised.

Contrary to heart disease, thirty years of intensive care research has yielded little literature showing differential treatment given to women. Critically ill men and women probably differ from each other in many

*Correspondence: helms.julie@icloud.com
[1] Faculté de Médecine, Université de Strasbourg (UNISTRA), Hôpitaux Universitaires de Strasbourg, Service de Médecine Intensive-Réanimation, Nouvel Hôpital Civil, Strasbourg, France
Full author information is available at the end of the article

ways [6]. Although differential access to intensive care for men and women has been described, it has not been shown in European countries [11]. Women have longer life expectancies than men which probably explains why female ICU patients were older and had higher SAPS II than did men. But if women are admitted to ICUs despite less favorable baseline characteristics, there is no reason to assume that men and women do not have equal access to ICU. Similarly, there is no reason to manage men and women differently when they are critically ill [12]. So why did the adjusted analysis suggest a lower probability of admission and poorer outcome for females when compared to males?

First, retrospective database analyses are always limited to the data they contain, therefore "silent" (unreported) variables are always a potential source of bias. The larger the dataset and the smaller the number of variables adjusted for—the larger the potential effect of such bias if it does exist. The information regarding hospital admissions was extracted from two very large databases (the Swiss Federal Office of Statistics and the Minimal Dataset for MDSi—ICU Registry) [13]. Both the Swiss ICU-Registry and Swiss Federal Office of Statistics have a limited set of variables, as do many databases. The analysis presented included a very small number of variables in relation to the number of cases, therefore underfitting may be an issue despite the best efforts of the authors.

Second, important clinical variables which should ideally have been included in the model were not available in either database (Table 1). Examples include comorbidities and chronic diseases prior to hospital admission. Lacking adjustment for these variables, gender effect, which may be only a confounder, may be misinterpreted as the cause for the differences observed. The prevalence of quite a few chronic conditions is higher among males than among females, and particularly among females of similar age. For example, the authors informed us that 7% of individuals aged > 50 years in Switzerland suffer from cardiovascular disease and that it is more prevalent in men than in women (source: National Health Report 2015, Swiss Health Observatory). Other chronic conditions may be more prevalent in women. Without adjusting for all of these components separately and elucidating the interaction between them, it is difficult to know what may have affected the outcome.

Third, with regards to the use of the SAPS II score; this score was also only available for ICU patients. In addition, only three previous health conditions are included in the SAPS II—whether the patient had metastatic carcinoma, hematological malignancies or AIDS. Therefore, adjusting the mortality prediction model to the SAPS II is no substitute adjustment to chronic conditions and their severity. The SAPS II includes 12 physiological variables that reflect patient acuity. However, the score was also included in the model as a whole, rather than with its separate components. Adjustment for pooled data essentially eliminates the possibility of identifying important individual factors.

Finally, the model also includes the nine equivalents of nursing manpower use (NEMS) score which measures the burden of nursing care. While it is true that mechanical ventilation, continuous renal replacement therapy and the use of vasoactive drugs are all used in patients that are more sick, these interventions are only surrogates for patient acuity.

Seeking inequality is the first step in combating inequality. Yet when inequality is sought in places where it is not obvious, the search is often initially accompanied by derision. Todorov et al. [10] have drawn our attention to the possibility, remote as it seems, of unequal access to intensive care among men and women in Europe. Several methodological aspects of their study raise hope that their findings may yet turn out to be a false alarm. However, these authors have thrown a stone into the pond of intensive care. Further research must be conducted to elicit the reasons for their findings if we are to determine that the ripples they have created can easily be stilled.

Table 1 Gender differences in characteristics that may have confounded the analysis of Todorov et al. [10]

Male–female differences	Explanations	References
Prior condition	Severity and comorbidity indexes according to the Cumulative Illness Rating Scale (CIRS-s and CIRS-c) were higher in men, while cognitive impairment, mood disorders, and disability in daily life were worse in women	[14]
	Women were older than men and had a higher prevalence of co-morbidities. After adjustment for co-morbidities, there was no significant gender difference in the use of drug-eluting stent	[15]
	Male gender and higher education level were associated with being less frail in planned ICU admissions	[16]
	Disability was 1.5 times more common in females, and was positively associated with increasing age	[14]
	ICU admission rates were similar for men and women after adjustment for age-related proportions of men versus women in the population served by each hospital and for co-morbid conditions	[17]
Disease clinical presentation and severity	Women with heart failure are more symptomatic than their male counterparts	[7]
	At the index age of 45 years, the lifetime risk for any heart failure through 90 years of age was higher in men than women. However, among heart failure subtypes, the lifetime risk for heart failure with reduced left ventricular ejection fraction was twice higher in men than women. In contrast, the lifetime risk for heart failure with preserved ejection fraction was similar in men and women	[18]
	This systematic review reported higher unadjusted mortality for women compared with men after acute myocardial infarction, although many of these differences were attenuated by adjustment for age	[1]
	Interactions between gender and treatment may also explain why women have similar mortality risk as men after revascularization	[1]
	Cardiovascular diseases are characterized by complex genetic traits with phenotypes being influenced by genetic factors, hormonal status, environmental factors, ethnicity and cultural variables	[2]
	Aetiologias, disease presentation and natural history of heart failure differ between women and men	[3]
	While female patients were older than men and had significantly less frequent anticoagulation therapy before onset of stroke and more severe NIHSS scores, there were no sex differences in the treatment outcomes at 90 days after stroke with non-valvular atrial fibrillation	[4]
	Women with heart disease wait longer before seeking treatment following an acute myocardial infarction	[19, 20]
Family request may differ in relation to treatment	After adjustment for severity of disease and outcome, ICU treatment differs between men and women. Men were more likely than women to undergo tracheostomy and ECMO	[12]
	Women were more likely to be discharged or die after a change in code status from full code whereas men were more likely to be discharged from the ICU or die with a full code status designation	[21]
Socio-economic variables	In all but one study, education and wealth levels were inversely associated with disability rates	[14]
	Directionality of effect when related to sex is unpredictable. In this study female sex was independently associated with fewer admissions to CCU/ICU, but the with risk of admission increasing incrementally as socioeconomically status declined	[22]
	Disparities in access to medical and device-based therapies may contribute to the greater symptom burden identified in women with heart failure	[7]
Research on the effects of drugs and intervention	Important sex-based disparities exist in enrollment in clinical trials. Women are indeed under-represented in clinical trials, especially pregnant and breastfeeding ones	[3, 7]
	Drug metabolism, efficacy and safety of frequently prescribed drugs such as analgesics, tranquillizers, statins and beta-blockers differ between women and men	[8]
	Research on the specific effects of gender on pharmacokinetics and pharmacodynamics are scarce, because female animals and women are under-represented in the pharmacological domain. Influence of gender on placebo effect, adherence to treatments, and drug safety profiles, is discussed	[9]

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06420-3.

Author details
[1] Faculté de Médecine, Université de Strasbourg (UNISTRA), Hôpitaux Universitaires de Strasbourg, Service de Médecine Intensive-Réanimation, Nouvel Hôpital Civil, Strasbourg, France. [2] Laboratoire d'ImmunoRhumatologie Moléculaire, Faculté de Médecine, Institut National de la Santé et de la Recherche Médicale (INSERM)UMR_S 1109, Institut Thématique Interdisciplinaire (ITI) de Médecine de Précision de Strasbourg, Transplantex NGFédération Hospitalo-Universitaire OMICARE, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Université de Strasbourg, Strasbourg, France. [3] Department of Anesthesia and Intensive Care Unit, Regional University Hospital of Montpellier, St-Eloi Hospital, University of Montpellier, PhyMedExp, INSERM U1046, CNRS UMR, 9214, CEDEX 5 Montpellier, France. [4] University Faculty of Medicine, Intensive Care Unit of the Shaare Zedek Medical Medical Centre and 2Hebrew, Jerusalem, Israel.

Compliance with ethical standards

Conflict of interests
The authors declares that they have no conflict of interests.

Publisher's Note

Received: 30 March 2021 Accepted: 21 April 2021
Published online: 5 May 2021

References

1. Bucholz EM, Butala NM, Rathore SS, Dreyer RP, Lansky AJ, Krumholz HM (2014) Sex differences in long-term mortality after myocardial infarction: a systematic review. Circulation 130:757–767
2. Winham SJ, de Andrade M, Miller VM (2015) Genetics of cardiovascular disease: importance of sex and ethnicity. Atherosclerosis 241:219–228
3. De Bellis A, De Angelis G, Fabris E, Cannata A, Merlo M, Sinagra G (2020) Gender-related differences in heart failure: beyond the "one-size-fits-all" paradigm. Heart Fail Rev 25:245–255
4. Okada T, Uchida K, Sakakibara F, Kageyama H, Yasaka M, Toyoda K, Mori E, Hirano T, Hamasaki T, Yamagami H, Nagao T, Uchiyama S, Minematsu K, Yoshimura S (2021) Sex differences in management and outcomes of cardioembolic stroke: post HOC analyses of the RELAXED study. J Stroke Cerebrovasc Dis: Off J Natl Stroke Assoc 30:105613
5. Vervloet M, Korevaar JC, Leemrijse CJ, Paget J, Zullig LL, van Dijk L (2020) Interventions to improve adherence to cardiovascular medication: what about gender differences? A systematic literature review. Patient Prefer Adherence 14:2055–2070
6. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, De Vries GJ, Epperson CN, Govindan R, Klein SL, Lonardo A, Maki PM, McCullough LD, Regitz-Zagrosek V, Regensteiner JG, Rubin JB, Sandberg K, Suzuki A (2020) Sex and gender: modifiers of health, disease, and medicine. Lancet 396:565–582
7. Punnoose LR, Lindenfeld J (2020) Sex-specific differences in access and response to medical and device therapies in heart failure: state of the art. Prog Cardiovasc Dis 63:640–648
8. Farkouh A, Riedl T, Gottardi R, Czejka M, Kautzky-Willer A (2020) Sex-Related differences in pharmacokinetics and pharmacodynamics of frequently prescribed drugs: a review of the literature. Adv Ther 37:644–655
9. Franconi F, Campesi I (2014) Sex and gender influences on pharmacological response: an overview. Expert Rev Clin Pharmacol 7:469–485
10. Todorov A, Kaufmann F, Arslani K, Haider A, Bengs S, Goliasch G, Zellweger N, Tontsch J, Sutter R, Buddeberg B, Hollinger A, Zemp E, Kaufmann M, Siegemund M, Gebhard C, Gebhard C (2021) Gender differences in the provision of intensive care: a bayesian approach. Intensive Care Med. https://doi.org/10.1007/s00134-00021-06393-00133
11. Fowler RA, Sabur N, Li P, Juurlink DN, Pinto R, Hladunewich MA, Adhikari NK, Sibbald WJ, Martin CM (2007) Sex-and age-based differences in the delivery and outcomes of critical care. CMAJ 177:1513–1519
12. Blecha S, Zeman F, Specht S, Lydia Pfefferle A, Placek S, Karagiannidis C, Bein T (2020) Invasiveness of treatment is gender dependent in intensive care results from a retrospective analysis of 26,711 cases. Anesth Analg. https://doi.org/10.1213/ANE.0000000000005082
13. Perren A, Cerutti B, Kaufmann M, Rothen HU (2019) A novel method to assess data quality in large medical registries and databases. Int J Qual Health Care: J Int Soc Qual Health Care 31:1–7
14. Corrao S, Argano C, Natoli G, Nobili A, Corazza GR, Mannucci PM, Perticone F, Investigators R (2019) Sex-differences in the pattern of comorbidities, functional independence, and mortality in elderly inpatients: evidence from the RePoSI register. J Clin Med 8(1):81
15. Iyanoye A, Moreyra AE, Swerdel JN, Gandhi SK, Cabrera J, Cosgrove NM, Kostis JB, Group MS (2015) Gender disparity in the use of drug-eluting stents during percutaneous coronary intervention for acute myocardial infarction. Catheter Cardiovasc Interv 86:221–228
16. Geense W, Zegers M, Dieperink P, Vermeulen H, van der Hoeven J, van den Boogaard M (2020) Changes in frailty among ICU survivors and associated factors: results of a one-year prospective cohort study using the Dutch clinical frailty scale. J Crit Care 55:184–193
17. Dodek P, Kozak JF, Norena M, Wong H (2009) More men than women are admitted to 9 intensive care units in British Columbia. J Crit Care 24(630):e631-638
18. Pandey A, Omar W, Ayers C, LaMonte M, Klein L, Allen NB, Kuller LH, Greenland P, Eaton CB, Gottdiener JS, Lloyd-Jones DM, Berry JD (2018) Sex and race differences in lifetime risk of heart failure with preserved ejection fraction and heart failure with reduced ejection fraction. Circulation 137:1814–1823
19. Mnatzaganian G, Braitberg G, Hiller JE, Kuhn L, Chapman R (2016) Sex differences in in-hospital mortality following a first acute myocardial infarction: symptomatology, delayed presentation, and hospital setting. BMC Cardiovasc Disord 16:109
20. Gibler WB, Armstrong PW, Ohman EM, Weaver WD, Stebbins AL, Gore JM, Newby LK, Califf RM, Topol EJ, Global Use of Strategies to Open Occluded Coronary Arteries I (2002) Persistence of delays in presentation and treatment for patients with acute myocardial infarction: the GUSTO-I and GUSTO-III experience. Ann Emerg Med 39:123–130
21. Purcell LN, Tignanelli CJ, Maine R, Charles A (2020) Predictors of change in code status from time of admission to death in critically Ill surgical patients. Am Surg 86:237–244
22. Mnatzaganian G, Hiller JE, Fletcher J, Putland M, Knott C, Braitberg G, Begg S, Bish M (2018) Socioeconomic gradients in admission to coronary or intensive care units among Australians presenting with non-traumatic chest pain in emergency departments. BMC Emerg Med 18:32