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Seasonality in the adverse outcomes in weight loss surgeries

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Abstract

Background: Weight loss surgery is a common procedure in the United States.

Objective: As weight loss surgery is largely an elective procedure for which patients and physicians can choose the timing, it could be helpful to explore the seasonality pattern of its perioperative adverse outcomes to help decide the timing of this surgery.

Setting: United States.

Methods: We used an obese adult sample (age ≥ 20 yr) of patients who underwent weight loss surgeries from the Premier Healthcare Database from 2011 to 2014. The International Classification of Diseases, Ninth Revision Clinical Modification procedure codes were used to identify weight loss surgery cases. Binary variables are used for 4 adverse outcomes, including hospital mortality, sepsis, deep vein thrombosis (DVT), and pulmonary embolism. The associations between the adverse outcomes and season of surgery were examined using logistic regressions, adjusting for age, sex, race, marital status, surgery types, body mass index, the Charlson co-morbidity index, and region.

Results: A total of 69,365 weight loss surgeries were identified for the analytic sample. The overall rate was .27% for hospital mortality, .16% for DVT, .10% for pulmonary embolism, and .20% for sepsis. For DVT, adjusted odds ratio for the fall was 2.68 (95% confidence interval: 1.39–5.19) and the odds ratio for the winter was 2.26 (95% confidence interval: 1.09–4.27) compared with the summer. For sepsis, adjusted odds ratio for the spring was 1.83 (95% confidence interval: 1.07–3.12) compared with that of the summer. The seasonality pattern was not statistically significant for hospital mortality and pulmonary embolism.

Conclusion: DVT and sepsis are more likely to occur in colder seasons compared with the summer season, although the crude rates of these adverse events were low. (Surg Obes Relat Dis 2018;14:291–296.) © 2018 Published by Elsevier Inc. on behalf of American Society for Metabolic and Bariatric Surgery.

One third of the U.S. adult population was obese in 2010, and 6.6% of Americans are estimated to be morbidly obese [1]. Many approaches are suggested to control or reduce excess weight, such as lifestyle changes, including

education, dietary modification, regular physical activity, and regular staff contacts with participants. However, these approaches can produce modest long-term weight loss of approximately 5% to 10% of starting weight [2]. Many patients select bariatric surgery as an effective option for treatment of substantial weight loss and improvement of obesity-related complications [3]. In 2013, an estimated 179,000 bariatric surgeries were performed in the United States, and the potential benefits of bariatric surgery are

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substantial [4]. Bariatric surgeries have been shown to be safe, with a low possibility of perioperative adverse outcomes [5]. For example, the 30-day postoperative mortality rate of bariatric surgery was .8 per 1000 based on a meta-analysis of randomized clinical trials published in 2014 [5]. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are 2 common causes of morbidity and mortality during and after bariatric surgery [6,7]. The reported postoperative rate of DVT varies widely from 2 to 13 per 1000 at 30 days among different subtypes of bariatric surgeries [6,8]. Factors that have been identified as increasing these adverse outcomes include certain surgery types, older age, and postoperative anastomotic leak [8].

As bariatric surgeries for weight loss are largely an elective procedure in which patients and physicians choose the time for surgery, it could be helpful to explore whether there is a temporal pattern of these perioperative adverse outcomes. Such a pattern, if found, could reduce the risk of complications, especially for those patients with existing conditions for adverse outcomes. Previous studies have shown seasonal pattern for the occurrence of PE and DVT among the general population [9,10]. In this study, we aimed to examine the seasonality pattern of the incidence of adverse outcomes among primary bariatric surgeries within the initial hospitalization, including hospital mortality, sepsis, DVT, and PE.

Methods

The Premier Database prospectively collected standard hospital discharge data (both outpatient and inpatient hospital visits) from more than 600 hospitals in the United States [11]. The Premier database included detailed information about procedures and medicine usage [11]. Using a subset of this database containing adult obese patients aged ≥ 20 years, we performed a retrospective study for those who underwent bariatric surgery from July 1, 2011 through June 3, 2014.

For our analysis, we included patients with body mass index (BMI) ≥ 30 kg/m² [12]. Participants were divided into 3 groups based on BMI categories: 30 to 34.9, 35 to 39.9, and ≥ 40 kg/m². Dependent variables were binary outcomes for each of the 4 adverse outcomes, and independent variables included age, race/ethnicity, sex, BMI categories, bariatric surgery subtypes, marital status, region, and seasons. Race/ethnicity was defined according to medical-record reporting; for simplicity, this variable was categorized as non-Hispanic white, non-Hispanic black, and others. Four seasons in a year were defined as spring (March–May), summer (June–August), fall (September–November), and winter (December–February), and summer was used as the reference level.

We used the International Classification of Diseases, Ninth Revision Clinical Modification procedure codes to identify bariatric surgery cases: 44.31 (high gastric bypass),

44.38 (laparoscopic gastroenterostomy), 44.39 (other gastroenterostomy), 44.68 (laparoscopic gastroplasty), 44.69 (other repair of stomach), 43.89 (open and other partial gastrectomy), 45.51 (isolation of segment of small intestine), 45.91 (small-to-small intestinal anastomosis), 43.7 (partial gastrectomy with anastomosis to jejunum), 44.38 (laparoscopic gastric bypass), 44.95 (laparoscopic gastric banding), and 43.82 (laparoscopic sleeve gastrectomy) to identify bariatric surgery patients [13–15]. Hospital death was identified by discharge status labeled as “expired” for the index surgery. Sepsis (995.91) [16], PE (415.1, 415.11, 415.12, 415.13, and 415.19) [17,18], and DVT (451.11, 451.19, 451.2, 451.81, 451.9, 453.40, 453.41, 453.42, 453.8, and 453.9) [19,20] were identified by the International Classification of Diseases, Ninth Revision diagnosis codes, respectively.

Four multivariate logistic regressions were used to examine the association between the seasons and the occurrence of hospital mortality, DVT, PE, and sepsis during the inpatient visits for bariatric surgery. We used Firth’s penalized likelihood method [21] for estimation given the sparse nature of these adverse events. We adjusted for patient age, sex, marital status, race/ethnicity, BMI categories before surgery (30–34.9, 35–39.9, and ≥ 40 kg/m²), type of bariatric surgery (open versus laparoscopic bariatric surgeries), and the Charlson co-morbidity index [22]. We used the 4 regions of the United States as the geographic covariates (northeast, midwest, south, and west). Statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC, USA). To address the possible issue of multiple inferences, we use the Dunnett’s multiplicity-adjusted confidence interval to determine the statistical significance in logistic regressions [23].

Results

We identified 69,365 bariatric operations in the Premier data set from 2011 to 2014. The median age of bariatric surgery recipients was 45 years (range, 20–89 yr), and approximately 95.00% aged from 20 to 65 years. Among them, 78.38% were female, 65.59% were non-Hispanic whites, 48.30% were married, and 79.32% had BMI ≥ 40 before the surgery (Table 1). In bariatric surgery patients, 90.04% surgeries were conducted under the assistance of laparoscope, and the most common bariatric surgery subtype was laparoscopic sleeve gastrectomy (41.56%), followed by laparoscopic gastric bypass (37.48%), and laparoscopic gastric banding (10.22%). Among the bariatric procedures, 27.85% were in spring, 27.30% were in summer, 21.50% were in fall, and 23.09% were in winter. There were statistically significant differences between the 4 seasons for the following variables: DVT, number of bariatric surgery patient, types of surgery, median age, marital status, and BMI. In particular, open surgery accounted for 13.34% in summer (the highest), while only

Table 1
Characteristics of bariatric surgery in PREMIER data from 2011–2014

	Total	Spring	Summer	Fall	Winter	<i>P</i> value
Total # of procedures	69,365	19,369	18,988	14,951	16,057	
% of procedures	100.00	27.85	27.30	21.50	23.09	<.0001
Adverse outcomes, %						
Hospital mortality	.27	.29	.30	.25	.22	.4219
Deep vein thrombosis	.16	.15	.09	.25	.19	.0034
Pulmonary embolism	.10	.11	.09	.09	.09	.9308
Sepsis	.20	.26	.16	.21	.18	.1881
Type of surgery, %						<.0001
Laparoscopic surgery	90.04	92.32	86.66	89.12	92.16	
Open surgery	9.96	7.68	13.34	10.88	7.84	
Characteristics						
Age, yr, median (range)	45 (20–89)	44 (20–89)	44 (20–89)	45 (20–89)	45 (20–89)	<.0001
20–65 yr	95.00	95.44	94.71	94.97	95.00	.09
> 65 yr	5.00	4.56	5.29	5.03	5.00	
Female, %	78.38	78.26	78.92	78.40	77.86	.11
Race/ethnicity, %						.09
Non-Hispanic White	65.59	65.54	66.13	65.25	65.51	
Non-Hispanic Black	14.49	14.78	13.92	14.28	14.82	
Other	19.92	19.68	19.94	20.47	19.68	
Marital status, %						.0007
Married	48.30	48.65	47.83	48.03	48.69	
Unmarried	35.92	36.36	35.87	35.41	35.94	
Others	15.78	14.99	16.30	16.57	15.37	
BMI, kg/m ² , %						.0023
30–34.9	2.76	2.85	2.43	2.74	3.06	
35–39.9	17.92	18.05	18.09	18.14	17.35	
≥40	79.32	79.10	79.49	79.11	79.59	
CCI mean ± SD	.42 ± .87	.43 ± .90	.41 ± .83	.42 ± .86	.43 ± .89	.07

BMI = body mass index; CCI = Charlson co-morbidity index; SD = standard deviation.

covering approximately 7.68% in spring (the lowest). The differences for hospital mortality, PE, sepsis, sex, race, co-morbidities (indexed by the Charlson co-morbidity index), and age group (20–65 years versus >65 years) between the 4 seasons were not statistically significant.

The overall rate was .27% for hospital mortality, .16% for DVT, .10% for PE, and .20% for sepsis (Table 1). For DVT, the highest rate was found in the fall (.25%), followed by winter (.19%), spring (.15%), and summer (.09%). Compared with surgeries performed during the summer, surgeries performed during the other 3 seasons are all positively associated with having DVT (fall, odds ratio [OR] = 2.68 with Dunnett-adjusted 95% confidence interval [CI] 1.39–5.19, *P* = .0015; spring, OR = 1.80 with Dunnett-adjusted 95% CI .88–3.49, *P* = .13; winter, OR = 2.26, with Dunnett-adjusted 95% CI 1.09–4.27, *P* = .024) although the adjusted difference between spring and summer was not statistically significant (Table 2). For sepsis, the highest rate was observed in spring (.26%), followed by fall (.21%), winter (.18%), and summer (.16%). After adjusting for other factors, the OR of sepsis was 1.83 (Dunnett-adjusted 95% CI: 1.07–3.12, *P* = .02) for spring compared with that of summer. For sepsis, the OR was 1.31 (Dunnett-adjusted 95% CI .73–2.35, *P* = .055) for fall; the OR was 1.27 (Dunnett-adjusted 95% CI .70–2.31, *P* = .67)

for winter compared with summer. The seasonal difference was not statistically significant for hospital mortality or PE in both crude rate and adjusted ORs.

Discussion

In this study of large sample size, we found that DVT and sepsis are more likely to occur in colder seasons compared with the warmer seasons among the 4 adverse outcomes, while the seasonal pattern was not significant for hospital mortality and PE. The seasonality pattern has been consistently identified in many health outcomes (especially cardiovascular outcomes), with the higher rates of adverse events occurring in colder months of the year [24,25]. Although the mechanism for these differences needs further investigation, our study is among the first to find the significant seasonal differences in certain perioperative adverse outcomes after bariatric surgery, independent of individual's demographic characteristics, surgery type, and co-morbidity before surgery.

DVT is a severe condition in which a blood clot forms in one or more of the deep veins and is closely associated with increased morbidity and mortality [26,27]. Among previous studies investigating the association between seasons and the occurrence of DVT, the majority found a higher

Table 2
Adjusted odds ratios (OR) of hospital mortality, deep vein thrombosis, pulmonary embolism, and sepsis by seasons (N = 69,365)

	Hospital mortality		Deep venous thrombosis		Pulmonary embolism		Sepsis	
	Adjusted rate (per 1000)	Adjusted OR (95% CI)	Adjusted rate (per 1000)	Adjusted OR (95% CI)	Adjusted rate (per 1000)	Adjusted OR (95% CI)	Adjusted rate (per 1000)	Adjusted OR (95% CI)
	Four seasons							
Fall	1.48 (0.95–2.33)	0.82 (.54–1.25)	2.64 (1.66–4.19)	2.68* (1.39–5.19)	1.60 (.86–2.95)	0.99 (.51–1.93)	3.46 (2.25–5.30)	1.31 (.80–2.14)
Summer	1.81 (1.20–2.73)	1.00 (reference)	.98 (.56–1.74)	1.00 (reference)	1.61 (0.91–2.84)	1.00 (reference)	2.63 (1.71–4.06)	1.00 (reference)
Spring	1.96 (1.30–2.96)	1.09 (.74–1.59)	2.12 (1.29–3.47)	1.80 (.88–3.49)	2.06 (1.19–3.58)	1.29 (.70–2.36)	4.82 (3.31–7.02)	1.88† (1.17–2.86)
Winter	1.40 (.88–2.23)	0.77 (.50–1.19)	1.73 (1.06–2.82)	2.26‡ (1.09–4.27)	1.67 (.90–3.10)	1.04 (0.54–2.03)	3.33 (2.14–5.20)	1.27 (.77–2.09)

CI = confidence interval.

ORs are adjusted by age, sex, race, marital status, bariatric surgery types, BMI, geographic regions, and Charlson Co-morbidity Index.

* Adjusted $P < 0.01$ (the P values were adjusted with Dunnett-Hsu correction for multiple comparisons).

† Adjusted $P < 0.05$ (the P values were adjusted with Dunnett-Hsu correction for multiple comparisons).

occurrence of DVT in the colder seasons [28]. For example, a retrospective study conducted by Boulay et al. [29] in France that included 65,081 patients with a diagnosed DVT between 1995 and 1998 showed that the number of patients is far larger in the winter than in the summer. The possible explanations for this observation include atmospheric temperature, air pressure, and air pollution [28].

The seasonality pattern of sepsis in our study was consistent with a retrospective cohort study in the United States conducted by Danaï et al. [30] that investigated seasonal variation in sepsis using patients hospitalized between 1979 and 2003, using data from the National Hospital Discharge Survey. The higher occurrence rate in colder seasons may come from higher risk of infectious disease outbreaks in those seasons, as the influenza season and respiratory syncytial virus outbreak often overlap [31,32]. The lower level of vitamin D in patients during colder months [33–35] may also result in a higher risk of infection [36–38], including sepsis, as sepsis severity has been found to be positively associated with vitamin D deficiency among emergency department patients [39].

Conclusions

Our study reveals the significance of seasonality in predicting adverse postoperative outcomes in bariatric surgeries and thus provides evidence to help the decision making about the timing for these elective surgeries. For patients with elevated risks for DVT complications (e.g., chronic heart failure, long hours of physical inactivity, history of multiple pregnancies, or rheumatoid arthritis [27,40]) and sepsis (e.g., older age, immune system impairment, chronic or serious illness [41,42]), such precautionary awareness of the possible seasonality factor could be particularly important. On the other hand, because the crude rate for DVT was only .16%, the clinical implication of those statistically significant ORs we estimated might be limited.

One seemingly paradoxical result is that the summer season saw the highest crude mortality even though its difference from other seasons is not statistically significant after adjusting for other factors. As our results show, the summer season has by far the highest ratio of open surgeries (13.34% as compared with the 9.96% rate in all seasons), which could account for the statistically insignificant difference between the summer surgeries' crude mortality rate and other seasons' crude mortality rate. The reason for the occurrence of more open surgeries in the summer warrants further investigation.

Our study has its strength in that we used a large sample size covering 4 years of data from many hospitals across different regions of the United States. This large sample size compensates for weaknesses typically associated with a convenience sample (e.g., insufficient external validity). One limit of this study is that our analysis was based on a

hospital discharge database and thus is subject to the hospital system's potential reporting bias. For instance, hospitals might choose not to charge for events such as sepsis because the provider could consider it as a medical error, as underreporting adverse events is not uncommon in the U.S. health systems [43]. However, our estimation of the seasonality pattern is unlikely to be substantially affected by this possible mechanism of underreporting adverse events as long as the underreporting does not vary across different seasons significantly.

Disclosure

The authors have no commercial associations that might be a conflict of interest in relation to this article.

References

- [1] Sturm R, Hattori A. Morbid obesity rates continue to rise rapidly in the United States. *Int J Obes (Lond)* Jun 2013;37(6):889–91.
- [2] Wing RR, Goldstein MG, Acton KJ, et al. Behavioral science research in diabetes: lifestyle changes related to obesity, eating behavior, and physical activity. *Diabetes Care* 2001;24(1):117–23.
- [3] Colquitt JL, Pickett K, Loveman E, Frampton GK. Surgery for weight loss in adults. *Cochrane Database Syst Rev* 2014;8:CD003641.
- [4] Schroeder R, Harrison TD, McGraw SL. Treatment of adult obesity with bariatric surgery. *Am Fam Physician* 2016;93(1):31–7.
- [5] Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. *JAMA Surg* 2014;149(3):275–87.
- [6] Froehling DA, Daniels PR, Mauck KF, et al. Incidence of venous thromboembolism after bariatric surgery: a population-based cohort study. *Obes Surg* 2013;23(11):1874–9.
- [7] Courcoulas AP, Christian NJ, O'Rourke RW, et al. Preoperative factors and 3-year weight change in the Longitudinal Assessment of Bariatric Surgery (LABS) consortium. *Surg Obes Relat Dis* 2015;11(5):1109–18.
- [8] Longitudinal Assessment of Bariatric Surgery Consortium, Flum DR, Belle SH, et al. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med* 2009;361(5):445–54.
- [9] Stein PD, Kayali F, Olson RE. Analysis of occurrence of venous thromboembolic disease in the four seasons. *Am J Cardiol* 2004;93(4):511–3.
- [10] Guijarro R, Trujillo-Santos J, Bernal-Lopez MR, et al. Trend and seasonality in hospitalizations for pulmonary embolism: a time-series analysis. *J Thromb Haemost* 2015;13(1):23–30.
- [11] Makadia R, Ryan PB. Transforming the premier perspective hospital database into the Observational Medical Outcomes Partnership (OMOP) common data model. *EGEMS (Wash DC)* 2014;2(1):1110.
- [12] Sturm R. Increases in morbid obesity in the USA: 2000-2005. *Public Health* 2007;121(7):492–6.
- [13] Kuo LE, Simmons KD, Williams NN, Kelz RR. Variation in the use of minimally invasive bariatric surgery. *Surg Obes Relat Dis* 2016;12(1):144–9.
- [14] Nguyen NT, Vu S, Kim E, Bodunova N, Phelan MJ. Trends in utilization of bariatric surgery, 2009-2012. *Surg Endosc* 2016;30(7):2732–7.
- [15] Kohn GP, Galanko JA, Overby DW, Farrell TM. Recent trends in bariatric surgery case volume in the United States. *Surgery* 2009;146(2):375–80.
- [16] Ramanathan R, Leavell P, Stockslager G, Mays C, Harvey D, Duane TM. Validity of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) screening for sepsis in surgical mortalities. *Surg Infect (Larchmt)* 2014;15(5):513–6.
- [17] Masotti L, Vannucchi V, Poggi M, Landini G. Trends in length of hospital stay in acute pulmonary embolism over the years. What is changing in the era of direct oral anticoagulants? *J Cardiovasc Med (Hagerstown)* 2017;18(7):556–9.
- [18] Raffini L, Huang YS, Witmer C, Feudtner C. Dramatic increase in venous thromboembolism in children's hospitals in the United States from 2001 to 2007. *Pediatrics* 2009;124(4):1001–8.
- [19] Wu CS, Lin CC, Chang CM, et al. Antipsychotic treatment and the occurrence of venous thromboembolism: a 10-year nationwide registry study. *J Clin Psychiatry* 2013;74(9):918–24.
- [20] Tamariz L, Harkins T, Nair V. A systematic review of validated methods for identifying venous thromboembolism using administrative and claims data. *Pharmacoepidemiol Drug Saf* 2012;21(Suppl 1):154–62.
- [21] Heinze G. A comparative investigation of methods for logistic regression with separated or nearly separated data. *Stat Med* 2006;25(24):4216–26.
- [22] Kieszak SM, Flanders WD, Kosinski AS, Shipp CC, Karp H. A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. *J Clin Epidemiol* 1999;52(2):137–42.
- [23] Westfall PH, Tobias RD, Wolfinger RD. Multiple comparisons and multiple tests using SAS. *Chesterbrook: SAS Institute*, 2011.
- [24] Yang L, Li L, Lewington S, et al. Outdoor temperature, blood pressure, and cardiovascular disease mortality among 23 000 individuals with diagnosed cardiovascular diseases from China. *Eur Heart J* 2015;36(19):1178–85.
- [25] Hopstock LA, Barnett AG, Bona KH, Mannsverk J, Njolstad I, Wilsgaard T. Seasonal variation in cardiovascular disease risk factors in a subarctic population: the Tromso Study 1979-2008. *J Epidemiol Community Health* 2013;67(2):113–8.
- [26] Edmonds MJ, Crichton TJ, Runciman WB, Pradhan M. Evidence-based risk factors for postoperative deep vein thrombosis. *ANZ J Surg* 2004;74(12):1082–97.
- [27] Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med* 2000;160(6):809–15.
- [28] Damjanovic Z, Jovanovic M, Stojanovic M. Correlation between the climatic factors and the pathogenesis of deep vein thrombosis. *Hippokratia* 2013;17(3):203–6.
- [29] Boulay F, Berthier F, Schoukroun G, Raybaut C, Gendreike Y, Blaive B. Seasonal variations in hospital admission for deep vein thrombosis and pulmonary embolism: analysis of discharge data. *BMJ* 2001;323(7313):601–2.
- [30] Danai PA, Sinha S, Moss M, Haber MJ, Martin GS. Seasonal variation in the epidemiology of sepsis. *Crit Care Med* 2007;35(2):410–5.
- [31] Griffin MR, Coffey CS, Neuzil KM, Mitchel EF Jr., Wright PF, Edwards KM. Winter viruses: influenza- and respiratory syncytial virus-related morbidity in chronic lung disease. *Arch Intern Med* 2002;162(11):1229–36.
- [32] Tanner H, Boxall E, Osman H. Respiratory viral infections during the 2009-2010 winter season in Central England, UK: incidence and patterns of multiple virus co-infections. *Eur J Clin Microbiol Infect Dis* 2012;31(11):3001–6.
- [33] van der Wielen RP, Lowik MR, van den Berg H, et al. Serum vitamin D concentrations among elderly people in Europe. *Lancet* 1995;346(8969):207–10.
- [34] Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. *J Clin Endocrinol Metab* 1988;67(2):373–8.

- [35] McKenna MJ, Freaney R, Meade A, Muldowney FP. Hypovitaminosis D and elevated serum alkaline phosphatase in elderly Irish people. *Am J Clin Nutr* 1985;41(1):101–9.
- [36] Cannell JJ, Vieth R, Umhau JC, et al. Epidemic influenza and vitamin D. *Epidemiol Infect* 2006;134(6):1129–40.
- [37] Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 2009;169(4):384–90.
- [38] Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* 2010;91(5):1255–60.
- [39] de Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. *Crit Care* 2014;18(6):660.
- [40] Choi HK, Rho YH, Zhu Y, Cea-Soriano L, Avina-Zubieta JA, Zhang Y. The risk of pulmonary embolism and deep vein thrombosis in rheumatoid arthritis: a UK population-based outpatient cohort study. *Ann Rheum Dis* Jul 2013;72(7):1182–7.
- [41] Tayek CJ, Tayek JA. Diabetes patients and non-diabetic patients intensive care unit and hospital mortality risks associated with sepsis. *World J Diabetes* 2012;3(2):29–34.
- [42] Lu CX, Qiu T, Tong HS, Liu ZF, Su L, Cheng B. Peripheral T-lymphocyte and natural killer cell population imbalance is associated with septic encephalopathy in patients with severe sepsis. *Exp Ther Med* 2016;11(3):1077–84.
- [43] Roehr B. US hospital incident reporting systems do not capture most adverse events. *BMJ* 2012;344:e386.