**Disparities in lung protective ventilation in the United States**

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***Online Supplement***

**Supplementary Methods**

***Multiple imputation***

STATA/SE 14.2 was used for all multiple imputation (MI) analyses 1. Race/ethnicity was missing in 96 subjects, height was missing in 147 subjects, and tidal volume was missing in 738 subjects in the full dataset.

We assumed the mechanism for missingness was not dependent on the unobserved data. For example, a patient’s height was not missing because shorter people tended to have height recorded less frequently, a patient’s race was not missing because black patients were less likely to have their race recorded, and a patient’s tidal volume was not missing because patients receiving higher tidal volumes were less likely to have their tidal volumes recorded in the respiratory flowsheets. This was assumed because the variables with missing values are routinely collected and entered in the medical record by hospital staff. Study investigators used this medical record as the primary source of data abstraction. If hospital personnel did not enter a value for one of these fields, it was recorded as missing by study investigators. It seems unlikely that the missing data for these variables depended on the unobserved data, as in the examples above. Instead, it seems more plausible that these data were missing because of human error in the completeness of medical record keeping by hospital staff and that this did not depend on the missing variables themselves. For these reasons, we considered these data missing at random (MAR)2. Finally, we did not make any assumptions about the pattern of missingness and instead assumed that missingness was arbitrary3.

We used multiple imputation using chained equations (MICE) with the “augment” option to avoid perfect prediction as the imputation method3-5. Our imputation model included the primary outcome variable (tidal volume > 8 mL/kg PBW), our pre-specified covariables from the primary multivariable analyses (see Figure 3), and all variables predictive of the missing values (those variables differing [p < 0.05] between observations with vs without missing values for race/ethnicity, height, or set tidal volume)2. These values included insurance status, APACHE II score, SOFA score, medical history of heart failure, cancer, chronic kidney disease, or HIV infection, a trauma or endocrine admission diagnoses, the source of hospital admission, the ICU type, the hospital type, the presence of nutrition or acute lung injury protocols, or the presence of a daily plan of care (Table E10).We handled variables with skewed distributions by using mathematical transformations to approximate normal distributions prior to the imputation step. Once the imputation step was complete, we back-transformed these variables to their original scale2.

One or more of height, tidal volume, and race/ethnicity was missing in 833 of the 2,513 patients (33%). We used 40 imputations to exceed this 33% frequency of missing values4,6. The values from each imputation were similar to each other and to those from the complete cases, indicating the imputation model was appropriate and suggesting that the missing at random assumption was plausible in the context of this model (Table E11) 6.

We then completed data analysis using the same covariables and logistic regression method as in the complete case analyses for each imputation set and the results were pooled. The effect estimates from these steps were comparable to those obtained from the complete case analyses (Tables E12 & E13). This was also true when we varied the number of imputations varied from 10 – 40 (Tables E12 & E13).

The Stata commands for the imputation step and the completed data analysis / pooling steps are shown in Table E14.

**Effect Modification (Interaction) Analysis**

We used the methods of Matthews et al 7 to investigate the possibility of heterogeneity in the effect of gender on tidal volume > 8 ml/kg PBW by height categories. The following categories were tabulated:

* Proportion of women of lower height receiving tidal volume > 8 ml/kg PBW (265/604): 0.44
* Proportion of men of lower height receiving tidal volume > 8 ml/kg PBW (51/159): 0.32
* The effect of female gender on tidal volume choice (as a proportion) in shorter patients:
	+ 0.44 – 0.32 = 0.12
* Proportion of women of higher height receiving tidal volume > 8 ml/kg PBW (23/106): 0.22
* Proportion of men of higher height receiving tidal volume > 8 ml/kg PBW (96/726): 0.13
* The effect of female gender on tidal volume choice (as a proportion) in taller patients:
	+ 0.22 – 0.13 = 0.09
* The difference in the effect of female gender on tidal volume choice in shorter vs. taller individuals:
	+ 0.12 – 0.09 = 0.03

We then calculated the standard error for this difference in the effect of female gender on tidal volume choice in shorter vs. taller individuals8:

$$se \left(0.12-0.09\right)= \sqrt{\frac{0.12 ×(1-0.12)}{763}}+ \sqrt{\frac{0.09 ×(1-0.09)}{832}}=0.015$$

From here, the 95% confidence interval for the difference in the effect of female gender on tidal volume choice in shorter vs. taller individuals is 0.00 – 0.06. Since this confidence interval included zero, we conclude that there is no significant difference in the effect of female gender on tidal volume choice by category of height.

***Mediation Analysis***

Pearl’s mediation formula9 was employed to assess the extent to which shorter height mediates the effect of female gender on excessive tidal volume. In this analysis, the exposure (X) is female gender, the mediator (Z) is height < 5’7”, and the outcome (Y) is tidal volume > 8 ml/kg PBW. The mediation formula requires calculation of *E(Y|x,z)*:the expected proportion of patients with or without the exposure (X) and with or without the mediator (Z) but with the outcome of interest (Y), given by *gx,z*, and *E(Z|x)*:the expected proportion of patients with or without the exposure (X) but with the mediator (Z), given by *hx*. The formulas for calculating these parameters and the calculations themselves are given in Supplementary Tables E1 and E2. The results are summarized in Supplementary Tables E3 and E4.

Table E1. Parameters required for mediation analysis: formulas

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Number of observations** | **Exposure (X)\*** | **Mediator (Z)†** | **Outcome (Y)‡** | ***E(Y|x,z)* = *gx,z*** | ***E(Z|x)* = *hx*** |
| n1 | 0 | 0 | 0 | $$\frac{n\_{2}}{n\_{1}+ n\_{2}}= g\_{0,0}$$ | $$\frac{n\_{3}+ n\_{4}}{n\_{1}+ n\_{2 }+ n\_{3 }+ n\_{4}}= h\_{0}$$ |
| n2 | 0 | 0 | 1 |
| n3 | 0 | 1 | 0 | $$\frac{n\_{4}}{n\_{3}+ n\_{4}}=g\_{0,1}$$ |
| n4 | 0 | 1 | 1 |
| n5 | 1 | 0 | 0 | $$\frac{n\_{6}}{n\_{5}+ n\_{6}}=g\_{1,0}$$ | $$\frac{n\_{7}+ n\_{8}}{n\_{5}+ n\_{6 }+ n\_{7 }+ n\_{8}}= h\_{1}$$ |
| n6 | 1 | 0 | 1 |
| n7 | 1 | 1 | 0 | $$\frac{n\_{8}}{n\_{7}+ n\_{8}}=g\_{1,1}$$ |
| n8 | 1 | 1 | 1 |

\* x = 0 if gender = male, 1 if gender = female

† z = 0 if height ≥ 5’7”, z = 1 if height < 5’7”

‡ y = 0 if tidal volume ≤ 8 ml/kg PBW, y = 1 if tidal volume > 8 ml/kg PBW

Table E2. Parameters required for mediation analysis: calculations

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Number of observations** | **Exposure (X)** | **Mediator (Z)** | **Outcome (Y)** | ***E(Y|x,z)* = *gx,z*** | ***E(Z|x)* = *hx*** |
| 630 | 0 | 0 | 0 | $$g\_{0,0}= 0.132$$ | $$h\_{0}=0.180$$ |
| 96 | 0 | 0 | 1 |
| 108 | 0 | 1 | 0 | $$g\_{0,1}=0.321$$ |
| 51 | 0 | 1 | 1 |
| 83 | 1 | 0 | 0 | $$g\_{1,0}=0.217$$ | $$h\_{1}=0.851$$ |
| 23 | 1 | 0 | 1 |
| 339 | 1 | 1 | 0 | $$g\_{1,1}=0.439$$ |
| 265 | 1 | 1 | 1 |

Table E3. Percentage of patients with tidal volume > 8 ml/kg PBW depending on whether or not female gender (X) and height < 5’7” (Z) are present (*gx,z*)

|  |  |  |
| --- | --- | --- |
| **Female gender****X** | **height < 5’7”****Z** | **% getting high VT*****gx,z = E (Y|x,z)*** |
| yes | Yes | **g1,1** = 44% |
| yes | No | **g1,0** = 22% |
| no | Yes | **g0,1** = 35% |
| no | No | **g0,0** = 13% |

Table E4. Percentage of patients with height < 5’7” (Z) depending on whether or not female gender (X) is present

|  |  |
| --- | --- |
| **Female gender** **X** | **% with height < 5’7” (Z)** ***hx = E(Z|x)***  |
| No | h0 = 18% |
| Yes | h1 = 85% |

These parameters in turn permit calculation of the *direct effect* of changing X on Y, the *indirect effect* of changing X on Y via the mediator Z, and the *total effect* of changing X on Y accounting for both the direct and indirect pathways. The formulas and results of these calculations given below. The analysis and interpretation of these effects are shown in Supplementary Table E5.

***Direct effect* (*DE*) = (*g1,0*– *g0,0*)(1 – *h0*) + (*g1,1*– *g0,1*) x *h0***

DE = (0.22 – 0.13)(1 – 0.18) + (0.44 – 0.32) x 0.18

DE = 0.09 x 0.82 + 0.12 x 0.18

DE = 0.074 + 0.022

**DE = 0.096 = 9.6%**

***Indirect effect* (*IE*) = (*h1* – *h0*)(*g0,1*– *g0,0*)**

IE = (0.85 – 0.18)(0.32 – 0.13)

IE = (0.67)(0.19)

**IE = 0.127 = 12.7%**

***Total effect* (*TE*) = [(*g1,1*x *h1*) + *g1,0*(1 – *h1*)] – [(*g0,1* x *h0*) + *g0,0*(1 – *h0*)]**

TE = [(0.44 x 0.85) + 0.22(1 – 0.85)] – [(0.32 x 0.18) + 0.13(1 – 0.18)]

TE = (0.37 + 0.03) – (0.058 + 0.11)

**TE = 0.40 – 0.168 = 0.232 = 23%**

Table E5. Analysis and interpretation

|  |  |
| --- | --- |
| **Effect calculations** | **Interpretation** |
| $$1- \frac{IE}{TE}=1-\frac{0.127}{0.230}= 0.055= 55\%$$ | 55 percent of instances of high tidal volume that are related to gender and/or height occur at least in part because female gender is having an effect. This does not exclude concomitant influences of short height on high tidal volume choice in these instances. |
| $$1- \frac{DE}{TE}=1- \frac{0.096}{0.23}= 0.58= 58\%$$ | 58 percent of instances of high tidal volume that are related to gender and/or height occur at least in part because short height is having an effect. This does not exclude concomitant direct influences of female gender on high tidal volume choice in these instances. |

**Additional Supplementary Tables**

Table E6. Hospital features by gender and insurance status\*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Study population****N = (1,595)** | **Women****(n = 710)** | **Men****(n = 885)** |  |  | **Underinsured****(n = 338)** | **Insured****(n = 1,257)** |
| **ICU type** |  |  |  |  |  |  |  |
|  Medical | 754 (47%) | 361 (51%) | 393 (44%) |  |  | 169 (50%) | 585 (46%) |
|  Surgical  | 185 (12%) | 83 (12%) | 102 (12%) |  |  | 15 (4%) | 170 (14%) |
|  Mixed | 335 (21%) | 151 (21%) | 184 (21%) |  |  | 81 (24%) | 254 (20%) |
|  Neurological / neurosurgical | 110 (7%) | 48 (7) | 62 (7) |  |  | 38 (12) | 72 (6) |
|  Trauma  | 92 (6) | 27 (4) | 65 (7) |  |  | 25 (7) | 67 (5) |
|  Cardiac / Cardiac surgery | 100 (6) | 37 (5) | 63 (7) |  |  | 7 (2) | 93 (7) |
|  Burn | 19 (1) | 3 (0.4) | 16 (2) |  |  | 3 (1) | 16 (1) |
|  |  |  |  |  |  |  |  |
| **Hospital type** |  |  |  |  |  |  |  |
|  Private (not-for-profit) | 961 (60%) | 450 (63%) | 511 (58%) |  |  | 169 (50) (49%) | 792 (63) |
|  Private (for profit) | 118 (7%) | 50 (7%) | 68 (8%) |  |  | 13 (4%) | 105 (8%) |
|  Public (non-federal) | 505 (32%) | 210 (30%) | 295 (33%) |  |  | 156 (46%) | 349 (28%) |
|  Federal | 11 (0.7%) | 0 (0%) | 11 (1%) |  |  | 0 (0%) | 11 (1%) |
|  |  |  |  |  |  |  |  |
| **Number of hospital beds** | 724 (496 – 885) | 724(453 – 873) | 746(511 – 885) |  |  | 724(453 – 873) | 746(496 – 885) |

\*Values refer to median (interquartile range) or number (percentage)

Table E7. Hospital features by race and ethnicity\*

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Race** | **Ethnicity** |
| **Variable** | **Study population****N = (1,595)** | **White (n = 1,113)** | **Black (n = 424)** | **Asian (n = 51)** | **American Indian / Alaska native (n = 7)** | **Non-Hispanic or Latino (n = 1,544)** | **Hispanic or Latino (n = 51)** |
| **ICU type** |  |  |  |  |  |  |  |
|  Medical | 754 (47%) | 498 (45) | 239 (56) | 15 (29) | 2 (28) | 723 (47) | 31 (60) |
|  Surgical  | 185 (12%) | 159 (14) | 22 (5) | 3 (6) | 1 (14) | 178 (12) | 7 (14) |
|  Mixed | 335 (21%) | 232 (21) | 82 (19) | 18 (35) | 3 (43) | 328 (21) | 7 (14) |
|  Neurological / neurosurgical | 110 (7%) | 64 (6) | 37 (9) | 9 (18) | 0 (0) | 105 (7) | 5 (10) |
|  Trauma  | 92 (6) | 59 (5) | 29 (7) | 4 (8) | 0 (0) | 91 (6) | 1 (2) |
|  Cardiac / Cardiac surgery | 100 (6) | 84 (8) | 14 (3) | 1 (2) | 1 (14) | 100 (6) | 0 (0) |
|  Burn | 19 (1) | 17 (2) | 1 (0.2) | 1 (2) | 0 (0) | 19 (1) | 0 (0) |
|  |  |  |  |  |  |  |  |
| **Hospital type** |  |  |  |  |  |  |  |
|  Private (not-for-profit) | 961 (60%) | 722 (65) | 194 (46) | 42 (82) | 3 (43) | 938 (61) | 23 (45) |
|  Private (for profit) | 118 (7%) | 101 (9) | 16 (4) | 0 (0) | 1 (14) | 115 (7) | 3 (6) |
|  Public (non-federal) | 505 (32%) | 280 (25) | 213 (50) | 9 (18) | 3 (43) | 480 (31) | 25 (49i) |
|  Federal | 11 (0.7%) | 9 (18) | 0 (0) | 0 (0) | 1 (14) | 11 (1) | 0 (0) |
|  |  |  |  |  |  |  |  |
| **Number of hospital beds** | 724 (496 – 885) | 750 (532 – 885) | 632 (318 – 885) | 724 (453 – 800) | 873 (411 – 953) | 746 (496 – 885) | 611 (283 – 755) |

\*Values refer to median (interquartile range) or number (percentage)

Table E8. Relationship of gender and tidal volume with covariables of interest

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  | ***Covariables of interest*** |  |
|  | **Age** | **# of comorbidities** | **Height (cm)** |  |
| **Gender** |  |  |  |
|  Women (n = 710) |  | 62 (52 – 73) | 1 (0 – 2) | 162 (157 – 167) |  |
|  Men (n = 885) |  | 60 (49 – 70) | 1 (0 – 1) | 177 (170 – 182) |  |
|  p value |  | 0.01 | 0.38 | < 0.001 |  |
| **Tidal volume**  |  |  |  |  |  |
|  Tidal volume > 8 ml/kg PBW (n = 466) |  | 62 (52 – 74) | 1 (0 – 1) | 162 (157 – 170) |  |
|  Tidal volume ≤ 8 ml/kg PBW (n = 1,214) |  | 60 (50 – 71) | 1 (0 – 2) | 173 (165 – 180) |  |
|  p value |  | 0.01 | 0.002 | < 0.001 |  |

Table E9. Relationship of race / ethnicity and tidal volume with covariables of interest

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Covariables of interest** |  |
|  | **Gender** | **Insurance Status** | **Number of comorbidities** |  |
|  |  | Men (n = 885) | Women n = 710) | Insured (n = 1,257) | Underinsured (n = 338)  |  |  |
| **Race** |  |  |  |  |  |  |  |
|  White (n = 1,113) |  | 640 (72) | 473 (67) | 953 (76) | 160 (47) | 1 (0 – 1) |  |
|  Black (n = 424) |  | 209 (24) | 215 (30) | 260 (21) | 164 (48) | 1 (0 – 2) |  |
|  Asian (n = 51) |  | 33 (4) | 18 (2) | 40 (3) | 11 (3) | 0 (0 – 1) |  |
|  American Indian / Alaska native (n = 7) |  | 3 (0.3) | 4 (0..6) | 4 (0.3) | 3 (0.9) | 1 (0 – 2) |  |
|  p value |  | 0.01 | < 0.001 |  0.01 |  |
| Ethnicity |  |  |  |  |  |  |  |
|  Non-hispanic or Latino (n = 1,544) |  | 859 (97) | 685 (96) | 1,224 (97) | 320 (95) | 1 (0 – 2) |  |
|  Hispanic or Latino (n = 51) |  | 26 (3) | 25 (4) | 33 (3) | 18 (5) | 0 (0 – 1) |  |
|  P value |  | 0.51 | 0.01 | 0.02 |  |
| **Tidal volume** |  |  |  |  |  |  |  |
|  Tidal volume ≤ 8 ml/kg PBW (n = 1,160)  |  | 738 (83) | 422 (59%) | 927 (74) | 233 (69%) | 1 (0 – 2) |  |
|  Tidal volume > 8 ml/kg PBW (n = 435) |  | 147 (17) | 288 (40%) | 330 (26) | 105 (31%) | 1 (0 – 1) |  |
|  p value |  | < 0.001 | 0.08 | 0.002 |  |

Table E10. Relationship of insurance status and tidal volume with covariables of interest

|  |  |  |
| --- | --- | --- |
|  |  | **Covariables of interest** |
|  | **Age** | **ICU admission after elective surgery** | **Race** | **Ethnicity** | **comorbidities** |
|  |  | years | No (n = 1,4140 | Yes (n = 181) | White | Black | Asian | American Indian / Alaskan native | Non-Hispanic or Latino (n = 1,544) | Hispanic or Latino (n = 51) | number |
| **Insurance status** |  |  |  |  |  |  |  |  |  |  |  |
|  Underinsured  (n = 3338) |  | 52 (41 – 59) | 319 (22) | 19 (10) | 160 (14) | 164 (39) | 11 (22) | 3 (43) | 320 (21) | 18 (35) | 1 (0 – 1) |
|  Insured  (n = 1,257) |  | 64 (54 – 74) | 1,095 (77) | 162 (90) | 953 (86) | 260 (61) | 40 (78) | 4 (57) | 1,224 (79) | 33 (65) | 1 (0 – 2) |
|  p value |  | < 0.001 | < 0.001 | < 0.001 | 0.01 | < 0.001 |
| **Tidal volume** |  |  |  |  |  |  |  |  |  |  |  |
|  > 8 ml/kg PBW  (n = 435) |  | 62 (52 – 74) | 365 (26) | 70 (39) | 303 (27) | 115 (27) | 16 (31) | 1 (14) | 419 (27) | 16 (31) | 1 (0 – 1) |
|  ≤ 8 ml/kg PBW  (n = 1,160) |  | 60 (50 – 71) | 1,049 (74) | 111 (61) | 810 (73) | 309 (73) | 35 (69) | 6 (86) | 1,125 (73) | 35 (69) | 1 (0 – 2) |
|  p value |  | 0.01 | < 0.001 | 0.79 | 0.50 | 0.002 |

Table E11. Relationships between insurance status and tidal volume > 8 mL/kg PBW: sensitivity analysis excluding 689 Medicare patients

|  |  |  |
| --- | --- | --- |
|  | **Underinsured****(n = 338)** | **Insured (Medicare excluded)****(n = 568)** |
| Tidal volume (mL)\* | 450 (400 – 500) | 450 (400 – 500) |
| Tidal volume / PBW (mL/kg)\* | 7.1 (6.4 – 8.2) | 7.0 (6.2 – 8.0) |
| Tidal volume > 8 ml/kg PBW (%) | 29 | 27 |
| Unadjusted odds ratiofor receiving tidal volume > 8 ml/kg PBW† | 1.47 (1.04 – 2.09) | 1 (ref) |
| Adjusted odds ratiofor receiving tidal volume > 8 ml/kg PBW† | 1.71 (1.26 – 2.32) ‡ | 1 (ref) |

\*Values refer to median (interquartile range) or number (percentage)

† Values refer to odds ratio (95% confidence interval);

‡Adjusted for age (continuous), ICU admission after elective surgery, race, ethnicity, and total # of APACHE II comorbidities (0-5).

Table E12: Relationship between predictors of interest and tidal volume > 8 mL/kg PBW, including adjustment for SOFA score

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Insurance status** | **Gender** | **Race\*** | **Ethnicity\*** |
|  | **Underinsured vs insured**† | **Women vs****men**‡ | **Black vs****white** | **Asian vs****white** | **American Indian / Alaskan native****vs white** | **Hispanic vs non-Hispanic** |
| Odds ratio (95% confidence interval) | 1.53 (1.14 – 2.04) | 1.27 (0.91 – 1.75) | 0.86 (0.52 – 1.45) | 1.34 (0.64 – 2.77) | 0.36 (.0.06 – 2.30) | 1.07 (0.37 – 3.03) |

†Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, total # of APACHE II comorbidities (0-5), and SOFA score

‡ Adjusted for age (continuous), height (continuous), total # of APACHE II comorbidities (0-5), and SOFA score

\* Adjusted for sex, insurance status, total # of APACHE II comorbidities (0-5), and SOFA score

Table E13: Relationship between predictors of interest and tidal volume > 8 mL/kg PBW, including adjustment for presence or absence of acute lung injury\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Insurance status** | **Gender** | **Race\*\*** | **Ethnicity\*\*** |
|  | **Underinsured vs insured**† | **Women vs****men**‡ | **Black vs****white** | **Asian vs****white** | **American Indian / Alaskan native****vs white** | **Hispanic vs non-Hispanic** |
| Odds ratio (95% confidence interval) | 1.54 (1.14 – 2.07) | 1.26 (.090 – 1.76) | 0.86 (0.51 – 1.46) | 1.36 (0.66 – 2.79) | 0.35 (0.05 – 2.40) | 0.86 (0.27 – 2.73) |

\*The presence or absence of acute lung injury (now termed ARDS) was determined by site investigators by chart review. This was missing in 26 patients, leaving 1,569 patients.

†Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, # of APACHE II comorbidities (0-5), and presence / absence of acute lung injury

‡ Adjusted for age (continuous), height (continuous), total # of APACHE II comorbidities (0-5), and presence / absence of acute lung injury

\* Adjusted for sex, insurance status, total # of APACHE II comorbidities (0-5), and presence / absence of acute lung injury

Table E14: Relationship between predictors of interest and tidal volume > 8 mL/kg PBW, including adjustment for mode of mechanical ventilation\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Insurance status** | **Gender** | **Race\*\*** | **Ethnicity\*\*** |
|  | **Underinsured vs insured**† | **Women vs****men**‡ | **Black vs****white** | **Asian vs****white** | **American Indian / Alaskan native****vs white** | **Hispanic vs non-Hispanic** |
| Odds ratio (95% confidence interval) | 1.45 (1.08 – 1.95) | 1.26 (0.92 – 1.73) | 0.83 (0.52 – 1.32) | 1.15 (0.54 – 2.44) | 0.45 (0.08 – 2.35) | 1.00 (0.37 – 2.72) |

\*Mechanical ventilation modes were categorized as follows: assist control (n = 845), synchronized intermittent mandatory ventilation (n = 262), pressure support (n = 63), pressure control (n = 6), airway pressure release ventilation (n = 7), high frequency oscillatory ventilation (n = 0), pressure regulated volume control (n = 264), and other (n = 148)

†Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation

‡ Adjusted for age (continuous), height (continuous), total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation

\*\* Adjusted for sex, insurance status, total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation

Table E15: Relationship between predictors of interest and tidal volume > 8 mL/kg PBW using hierarchical modeling with patients nested within ICUs\*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Insurance status** | **Gender** | **Race\*\*** | **Ethnicity\*\*** |
|  | **Underinsured vs insured**† | **Women vs****men**‡ | **Black vs****white** | **Asian vs****white** | **American Indian / Alaskan native****vs white** | **Hispanic vs non-Hispanic** |
| Odds ratio (95% confidence interval) | 1.47 (1.05 – 2.06) | 1.34 (0.94 – 1.92) | 0.85 (0.61 – 1.20) | 1.09 (0.54 – 2.22) | 0.26 (0.19 – 3.67) | 1.79 (0.86 – 3.74) |

\*hierarchical models were generated using the “xtlogit” command in STATA 14 including ICU as a fixed effect. All four patients in one ICU had the same outcome prediction for tidal volume > 8 mL/kg PBW, so these observations were dropped from the model leaving 1,591 patients for analysis.

†Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation

‡ Adjusted for age (continuous), height (continuous), total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation

\*\* Adjusted for sex, insurance status, total # of APACHE II comorbidities (0-5), and mode of mechanical ventilation

Table E16. Patient Characteristics (all mechanically ventilated patients) and comparison of subjects with vs without missing values

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Study population****N = (2513)** | **Non-missing ht/vt****(n = 1,730)** | **Missing ht/ vt****(n = 783)** | **OR (95% CI)** | **Non-missing race ethnicity (n = 2,320)** | **Missing race or ethnicity (n = 193)** | **OR (95% CI)** |
| Age (years) | 61 (50 – 71) | 60 (50 – 71) | 61 (49 – 72) |  | 61 (50 – 71) | 55 (41 – 67) |  |
| Race |  |  |  |  |  |  |  |
|  White | 1620 (67) | 1,113 (70) | 571 (79) | 1.60 (1.30 – 1.99) |  |  |  |
|  Black |  | 424 (26) | 137 (19) | 0.64 (0.51 – 0.80) |  |  |  |
|  Asian |  | 51 (3) | 13 (2) | 0.55 (0.27 – 1.04) |  |  |  |
|  American Indian / Alaskan native |  | 7 (0.4) | 4 (0.6) | 1.26 (0.27 – 4.97) |  |  |  |
| Ethnicity |  |  |  | 0.52 (0.33 – 0.78) |  |  |  |
|  Non-hispanic | 2,354 (94) | 1,602 (93) | 752 (96) |  |  |  |  |
|  Hispanic | 159 (6) | 128 (7) | 31 (4) |  |  |  |  |
| Gender |  |  |  | 0.94 (0.79 – 1.11) |  |  | 0.73 (0.53 – 1.00) |
|  Men | 1413 (56) | 964 (55) | 449 (57) |  | 1,291 (56) | 122 (63) |  |
|  Women | 1,100 (43) | 766 (44) | 334 (43) |  | 1,029 (44) | 71 (37) |  |
| Insurance status |  |  |  | 0.67 (0.53 – 0.84) |  |  | 1.99(1.42 – 2.75) |
|  insured | 1,995 (79) | 1,340 (77) | 655 (84) |  | 1,865 (80) | 130 (67) |  |
|  Under-insured | 518 (21) | 390 (23) | 128 (16) |  | 455 (20) | 63 (33) |  |
| APACHE II score | 20 (15 – 25) | 21 (16 – 26) | 18 (13 – 22) |  | 20 (15 – 25) | 18 (14 – 24) |  |
| SOFA score | 6 (4 – 9) | 7 (4 – 10) | 5 (3 – 8) |  | 6 (4 – 9) | 6 (4 – 9) |  |
| Hospital mortality† |  |  |  | 0.76 (0.62 – 0.94) |  |  | 1.07 (0.76 – 1.50) |
|  No | 1,687 (72) | 1,136 (70) | 551 (76) |  | 1,552 (72) | 135 (71) |  |
|  Yes | 655 (28) | 478 (30) | 177 (24) |  | 599 (28) | 56 (29) |  |
| Hospital length of stay (days)† | 18 (10 – 30) | 17 (10 – 30) | 18 (11 – 30) |  | 17 (10 – 30) | 19 (12 – 31) |  |
| ICU length of stay (days)† | 10 (5 – 18) | 10 (5 – 18) | 11 (5 – 19) |  | 10 (5 – 18) | 13 (6 – 20) |  |
| Comorbid conditions |  |  |  |  |  |  |  |
|  Heart failure | 378 (15) | 287 (17) | 91 (12) | 0.66 (0.51 – 0.86) | 353 (15) | 25 (13) | 0.83 (0.51 – 1.29) |
|  COPD | 639 (25) | 449 (26) | 190 (24) | 0.91 (0.75 – 1.12) | 594 (26) | 45 (23) | 0.88 (0.61 – 1.26) |
|  Cancer | 557 (22) | 351 (20) | 206 (26) | 1.40 (1.14 – 1.72) | 531 (23) | 26 (13) | 0.52 (0.33 – 0.81) |
|  Chronic kidney disease | 375 (15) | 284 (16) | 91 (12) | 0.67 (0.51 – 0.87) | 348 (15) | 27 (14) | 0.92 (0.58 – 1.42) |
|  Chronic liver disease | 288 (11) | 208 (12) | 80 (10) | 0.83 (0.62 – 1.10) | 257 (11) | 31 (16) | 1.53 (0.99 – 2.32) |
|  HIV/AIDS | 75 (3) | 63 (4) | 12 (2) | 0.41 (0.20 – 0.78) | 71 (3) | 4 (2) | 0.67 (0.18 – 1.82) |
| Admission diagnosis category |  |  |  |  |  |  |  |
|  Respiratory | 1345 (54) | 937 (54) | 408 (52) | 0.92 (0.77 – 1.09) | 1,242 (53) | 103 (53) | 0.99 (0.73 – 1.35) |
|  Infectious | 723 (29) | 529 (30) | 203 (26) | 0.81 (0.67 – 0.99) | 660 (28) | 63 (32) | 1.22 (0.88 – 1.68) |
|  Cardiovascular | 709 (28) | 503 (29) | 206 (26) | 0.87 (0.72 – 1.06) | 663 (28) | 46 (23) | 0.78 (0.54 – 1.11) |
|  Gastrointestinal | 381 (15) | 264 (15) | 117 (15) | 0.98 (0.76 – 1.24) | 342 (15) | 39 (20) | 1.46 (0.98 – 2.13) |
|  Trauma | 207 (8) | 121 (7) | 86 (11) | 1.64 (1.21 – 2.21) | 180 (8) | 27 (13) | 1.93 (1.20 – 3.01) |
|  Endocrine | 139 (6) | 111 (6) | 28 (4) | 0.54 (0.34 – 0.83) | 128 (6) | 11 (6) | 1.04 (0.49 – 1.96) |
|  Other | 383 (15) | 257 (15) | 126 (16) | 1.10 (086 – 1.39) | 354 (15) | 29 (15) | 0.98 (0.63 – 1.49) |
| Admission source  |  |  |  |  |  |  |  |
|  Emergency department | 1,061 (42) | 776 (45) | 285 (36) | 0.70 (0.59 – 0.84) | 983 (42) | 78 (40) | 0.92 (0.67 – 1.25) |
|  Hospital floor | 515 (20) | 342 (20) | 173 (22) | 1.15 (0.93 – 1.42) | 475 (20) | 40 (21) | 1.02 (0.69 – 1.47) |
|  Operating room | 406 (16) | 267 (15) | 139 (18) | 1.18 (0.94 – 1.49) | 385 (17) | 21 (11) | 0.61 (0.36 – 0.98) |
|  Outside hospital | 415 (16) | 281 (16) | 134 (17) | 1.06 (0.84 – 1.34) | 370 (16) | 45 (23) | 1.60 (1.10 – 2.30) |
|  Other | 116 (5) | 64 (4) | 52 (7) | 1.85 (1.24 – 2.74) | 107 (5) | 9 (5) | 1.01 (0.44 – 2.04) |
| ICU type |  |  |  |  |  |  |  |
|  Medical | 1,178 (47) | 845 (49) | 333 (42) | 0.78 (0.65 – 0.92) | 1,081 (46) | 97 (50) | 1.16 (0.85 – 1.57) |
|  Surgical | 860 (34) | 536 (31) | 324 (41) | 1.57 (1.31 – 1.88) | 781 (34) | 79 (41) | 1.36 (1.00 – 1.86) |
|  Mixed | 475 (19) | 349 (20) | 126 (16) | 0.76 (0.60 – 0.95) | 458 (20) | 17 (9) | 0.39 (0.22 – 0.66) |
| Hospital type |  |  |  |  |  |  |  |
|  Private (not-for-profit) | 1,637 (65) | 1,036 (60) | 601 (77) | 2.21 (1.82 – 2.69) | 1,516 (65) | 121 (63) | 0.89 (0.65– 1.22,  |
|  Private (for profit) | 153 (6) | 121 (7) | 32 (4) | 0.57 (0.37 – 0.85) | 149 (6) | 4 (2) | 0.31 (0.08 – 0.82) |
|  Public (non-federal) | 708 (28) | 562 (32) | 146 (19) | 0.48 (0.38 – 0.59) | 640 (28) | 68 (35) | 1.43 (1.03 – 1.96) |
|  Federal | 15 (1) | 11 (0.6) | 4 (0.5) | 0.80 (0.19 – 2.72) | 15 (1) | 0 (0) | --- |
| Number of hospital beds | 687 (496 – 873) | 724 (496 – 885) | 615 (470 – 845) |  | 687 (470 – 873) | 724 (550 – 800) |  |
| Nutrition protocol | 1,515 (60) | 980 (57) | 535 (68) | 1.65 (1.38 – 1.98) | 1,210 (52) | 112 (59) | 1.31 (0.96 – 1.80) |
|  Acute lung injury protocol | 2,033 (81) | 1,364 (79) | 669 (85) | 1.57 (1.24 – 2.0) | 1,919 (83) | 114 (59) | 0.30 (0.22 – 0.42) |
| Daily plan of care | 2,138 (85) | 1,427 (82) | 711 (91) | 2.10 (1.59 – 2.79) | 1,974 (85) | 164 (85) | 0.99 (0.65 – 1.55) |

\* Values refer to median (interquartile range) or number (percentage)

† Mortality status, ICU length of stay, and hospital length of stay were missing in 171 patients.

Table E17. STATA 14, multiple imputation commands

|  |  |
| --- | --- |
| **Description** | **STATA command** |
| Format the data for multiple imputation | mi set wide |
| Register the variables with missing values that are to be imputed | mi register imputed race height3 square root of tidal volume  |
| The imputation model | mi impute chained (regress) height3 square root of tidal volume (logit) race = age sex comorbidities insurance status admission after elective surgery APACHE II score SOFA score heart failure cancer chronic kidney disease HIV infection trauma admission diagnosis endocrine admission diagnosis admission source ICU type hospital type nutrition protocol acute lung injury protocol daily plan of care, add(40) augment |
| Fit the model for each imputation and combine the results, gender is primary exposure variable | mi estimate: logistic tidal volume > 8 mL/kg sex age height comorbidities, vce (cluster site) |
| Fit the model for each imputation and combine the results, race is primary exposure variable | mi estimate: logistic tidal volume > 8 mL/kg race insurance status comorbidities, vce (cluster site) |
| Fit the model for each imputation and combine the results, insurance status is primary exposure variable | mi estimate tidal volume > 8 mL/kg insurance status age post-op from elective surgery race comorbidities |

†Adjusted for age (continuous), ICU admission after elective surgery, non-white vs white race/ethnicity, and total # of APACHE II comorbidities (0-5)

Table E18. Height, tidal volume, and race values from complete cases and each imputation

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Height** ‡ | **Tidal volume**‡ | Race (percent) |
|  | **(inches)** | **(mL)** | White | Black | Asian | American Indian / Alaska native |
| Actual\* | 66.5 (4.5) | 458 (88) | 72 | 24 | 3 | 0.5 |
| Imputation 1†  | 66.6 (4.5) | 462 (89) | 73 | 23 | 3 | 0.5 |
| Imputation 2 | 66.6 (45) | 462 (89) | 73 | 24 | 3 | 0.6 |
| Imputation 3 | 66.6 (4.5) | 461 (89) | 73 | 24 | 3 | 0.5 |
| Imputation 4 | 66.6 (4.5) | 460 (88) | 73 | 24 | 3 | 0.4 |
| Imputation 5 | 66.6 (4.5) | 461 (89) | 74 | 23 | 3 | 0.4 |
| Imputation 6 | 66.6 (4.5) | 459 (88) | 73 | 23 | 3 | 0.5 |
| Imputation 7 | 66.6 (4.5) | 460 (89) | 73 | 24 | 3 | 0.6 |
| Imputation 8 | 66.6 (4.5) | 461 (87) | 73 | 23 | 3 | 0.5 |
| Imputation 9 | 66.6 (4.5) | 461 (89) | 73 | 24 | 3 | 0.5 |
| Imputation 10 | 66.6 (4.5) | 461 (88) | 72 | 23 | 4 | 0.6 |
| Imputation 11 | 66.6 (4.5) | 459 (87) | 73 | 24 | 3 | 0.7 |
| Imputation 12 | 66.6 (4.5) | 461 (89) | 73 | 24 | 3 | 0.5 |
| Imputation 13 | 66.6 (4.5) | 460 (88) | 73 | 23 | 3 | 0.5 |
| Imputation 14 | 66.6 (4.5) | 460 (89) | 73 | 23 | 3 | 0.5 |
| Imputation 15 | 66.6. (4.5) | 459 (88) | 74 | 23 | 3 | 0.5 |
| Imputation 16 | 66.6 (4.5) | 461 (88) | 73 | 24 | 3 | 0.4 |
| Imputation 17 | 66.6 (4.5) | 460 (88) | 73 | 23 | 3 | 0.5 |
| Imputation 18 | 66.6 (4.5) | 461 (88) | 73 | 24 | 3 | 0.6 |
| Imputation 19 | 66.6 (4.5) | 460 (88) | 73 | 23 | 3 | 0.4 |
| Imputation 20 | 66.6 (4.5) | 459 (88) | 73 | 23 | 3 | 0.6 |
| Imputation 21 | 66.6 (4.5) | 459 (87) | 73 | 24 | 3 | 0.6 |
| Imputation 22 | 66.6 (4.5) | 459 (87) | 73 | 24 | 3 | 0.4 |
| Imputation 23 | 66.6 (4.5) | 461 (89) | 73 | 24 | 3 | 0.6 |
| Imputation 24 | 66.6 (4.5) | 461 (90) | 73 | 24 | 3 | 0.5 |
| Imputation 25 | 66.6 (4.5) | 459 (88) | 73 | 24 | 3 | 0.4 |
| Imputation 26 | 66.6 (4.5) | 461 (88) | 74 | 23 | 3 | 0.5 |
| Imputation 27 | 66.6 (4.5) | 459 (88) | 73 | 24 | 3 | 0.7 |
| Imputation 28 | 66.6 (4.5) | 459 (89) | 73 | 24 | 3 | 0.4 |
| Imputation 29  | 66.6 (4.5) | 460 (89) | 73 | 23 | 3 | 0.8 |
| Imputation 30 | 66.5 (4.5) | 461 (87) | 74 | 23 | 3 | 0.5 |
| Imputation 31 | 66.6 (4.5) | 460 (88) | 73 | 24 | 3 | 0.6 |
| Imputation 32 | 66.6 (4.5) | 459 (88) | 73 | 24 | 3 | 0.7 |
| Imputation 33 | 66.6 (4.5) | 461 (88) | 74 | 23 | 3 | 0.4 |
| Imputation 34 | 66.5 (4.5) | 460 (88) | 73 | 24 | 3 | 0.5 |
| Imputation 35 | 66.6 (4.5) | 458 (87) | 73 | 24 | 3 | 0.4 |
| Imputation 36 | 66.6 (4.5) | 460 (89) | 73 | 24 | 3 | 0.5 |
| Imputation 37 | 66.6 (4.5) | 460 (88) | 73 | 24 | 3 | 0.6 |
| Imputation 38 | 66.6 (4.5) | 460 (90) | 73 | 24 | 3 | 0.5 |
| Imputation 39 | 66.6 (4.5) | 462 (88) | 73 | 23 | 3 | 0.6 |
| Imputation 40 | 66.6 (4.5) | 459 (88) | 73 | 24 | 3 | 0.4 |

\* n = 2,366 for height, n = 1,824 for tidal volume, n = 2,320 for race

† imputations were performed for all 2,513 patients in the complete dataset

‡ results expressed as mean (standard deviation)

Table E19. Adjusted odds ratios for association between exposures of interest and tidal volume > 8 mL/kg PBW, all mechanically ventilated patients (n = 2,513)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Insurance status** | **Gender** | **Race\*** | **Ethnicity\*** |
|  | **Underinsured vs insured**† | **Women vs****men**‡ | **Black vs****white** | **Asian vs****white** | **American Indian / Alaskan native****vs white** | **Hispanic vs non-Hispanic** |
| Adjusted odds ratiofor receiving tidal volume > 8 ml/kg PBW10 imputations per missing value | 1.40 (1.08 – 1.82) | 1.39 (1.03 – 1.88) | 0.85 (0.56 – 1.30) | 1.34 (0.72 – 2.53) | 0.33 (0.06 – 1.72) | 1.17 (0.61 – 2.27) |
| Adjusted odds ratiofor receiving tidal volume > 8 ml/kg PBW30 imputations per missing value | 1.42 (1.09 – 1.85) | 1.38 (1.03 – 1.84) | 0.85 (0.55 – 1.32) | 1.32 (0.71 – 2.48) | 0.32 (0.05 – 2.27) | 1.25 (0.68 – 2.30) |
| Adjusted odds ratiofor receiving tidal volume > 8 ml/kg PBW40 imputations per missing value | 1.42 (1.06 – 1.89) | 1.37 (1.03 – 1.83) | 0.83 (0.53 – 1.29) | 1.30 (0.70 – 2.44) | 0.31 (0.05 – 2.01) | 1.24 (0.67 – 2.30) |
| Adjusted odds ratiofor receiving tidal volume > 8 ml/kg PBWfrom **primary complete case analysis** | 1.56 (1.16 – 2.10) | 1.28 (0.92 – 1.77) | 0.86 (0.52 – 1.41) | 1.30 (0.63 – 1.41) | 0.32 (0.05 – 2.00) | 1.08 (0.39 – 2.94) |

†Adjusted for age (continuous), ICU admission after elective surgery, race/ethnicity, and total # of APACHE II comorbidities (0-5)

‡ Adjusted for age (continuous), height (continuous), and total # of APACHE II comorbidities (0-5)

\* Adjusted for sex, insurance status, and total # of APACHE II comorbidities (0-5)

Table E20. Relationships between insurance status and tidal volume > 8 mL/kg PBW in all ventilated patients, multiple imputation analysis excluding 1,058 Medicare patients (n = 1,455)

|  |  |
| --- | --- |
|  | **Underinsured vs insured** † |
| Adjusted odds ratiofor receiving tidal volume > 8 ml/kg PBW10 imputations per missing value | 1.45 (1.09 – 1.93) |
| Adjusted odds ratiofor receiving tidal volume > 8 ml/kg PBW30 imputations per missing value | 1.49 (1.12 – 1.97) |
| Adjusted odds ratiofor receiving tidal volume > 8 ml/kg PBW40 imputations per missing value | 1.48 (1.09 – 2.02) |

†Adjusted for age (continuous), ICU admission after elective surgery, non-white vs white race/ethnicity, and total # of APACHE II comorbidities (0-5)

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