**Associations of macrovascular complications with death in patients with diabetes hospitalized for coronavirus disease-2019 (COVID-19)**

**Aim:** To assess whether the presence of macrovascular complications (ischemic heart disease, stroke, peripheral artery disease) are associated with mortality and severity outcomes in subjects with diabetes mellitus (DM) hospitalized for COVID-19 in a European multicenter observational study.

**Exposure variables:** The presence of macrovascular complications will be defined according to the presence of a previous history of ischemic heart disease (including history of myocardial infarction or heart failure), cerebrovascular disease (including history of stroke or transient ischemic attack - TIA-) and/or peripheral artery disease. Data will be processed as defined for each database of this collaborative proposal.

**Definition of the outcomes:**

* Primary endpoint: in-hospital mortality.
* Secondary outcomes: length of hospital stay, intensive care unit (ICU) admission and use of invasive mechanical ventilation (IMV) on admission.

**Statistical analysis:**

All data will be tested for normality using the Shapiro-Wilk test. Data will be presented as number (percentage) of participants for categorical variables, mean +/- standard deviation (SD) for normally distributed quantitative variables, or median (25th-75th percentile) for non-normally distributed quantitative variables. Differences between groups (presence vs. absence of macrovascular complications) will be analyzed using the x2 test for comparisons of proportions and unpaired t-tests or Mann-Whitney U tests for comparisons of normally and non-normally distributed quantitative variables, as needed. The association between the primary (mortality) and secondary endpoints (length of hospital stay, ICU admission and IMV on admission) and the presence of macrovascular complications will be assessed using logistic regression analyses (odds ratios). Kaplan-Meier curves will be generated to represent mortality by the absence/presence of macrovascular complications; log-rank test will be used to compare survival distributions. Association of macrovascular complications with hospital mortality will be assessed by unadjusted and adjusted (age and sex) Cox proportional hazards models. Results will be expressed as hazard ratio (HR) and 95% CI.  Two-tailed p-values <0.05 will be considered statistically significant.

**SKELETON TABLES FOR OTHER COUNTRIES’ DATA**

**Comparison of characteristics of people with complete and missing data for macrovascular complications**

|  |  |  |
| --- | --- | --- |
|  | Complete data (n=1846) | Missing data (n=1333) |
| Age (mean, SD) years  N missing | 72.5(13.9)  0 | 70.8(14.4)  6 |
| Sex, Men, n (%)  N missing | 1140 (62%)  0 | 802(60%)  5 |
| BMI  N missing | 29.3(7.2)  0 | 28.6(6.9)  860 |
| **Ethnicity:**  White n (%)  Asian n (%)  Black n (%)  Other n (%)  N missing | 1291(70%)  275(15%)  116(6%)  164(9%)  0 | 624(60%)  167(16%)  94(9%)  157(15%)  291 |
| **Type of diabetes**  Type 1 n (%)  Type 2 n (%)  N missing | 93(5%)  1753(95%)  0 | 62(5%)  1163(95%)  108 |
| Hypertension  N missing | 1286(70%)  0 | 774(66%)  166 |
| Dyslipidaemia  N missing | NA | NA |
| Microvascular disease  N missing | 807(44%)  0 | 242(39%)  710 |
| Death (in-hospital mortality) N missing | 715(39%)  0 | 524(39%)  0 |
| Length of hospital stay (mean, SD), days | NA | NA |
| ICU admission  N missing | 193(10%)  0 | 125(13%)  337 |
| Use of IMV  N missing | NA | NA |

**For COMPLETION by COLLABORATORS**

Table 1. Clinical characteristics of subjects according to macrovascular status(Complete dataset).

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All**  **(n=1846)** | **No MACRO (n=1042)** | **Any MACRO (n=804)** |
| Age (mean, SD) years | 72.5(13.9) | 69.1(14.8) | 76.8(11.2) |
| Sex(Men, n%) | 1140(62%) | 610(59%) | 530(66%) |
| **Ethnicity:**  White  Asian  Black  Other | 1291(70%)  275(15%)  116(6%)  164(9%) | 655(63%)  200(19%)  64(6%)  123(12%) | 626(79%)  75(9%)  52(6%)  41(6%) |
| **Type of diabetes**  Type 1  Type 2 | 93(5%)  1753(95%) | 59(6%)  983(94%) | 34(4%)  770(96%) |
| Smoking status  Never-  Former or current | 962(93%)  78(7%) | 471(92%)  41(8%) | 491(93%)  37(7%) |
| Hypertension | 1286(70%) | 713(68%) | 573(71%) |
| Dyslipidaemia | NA | NA | NA |
| BMI | 29.3(7.2) | 29.9(7.2) | 28.6(7.1) |
| Diabetes duration | NA | NA | NA |
| HbA1c mmol/mol, mean(SD) | 62(22) | 63(23) | 62(21) |
| Microvascular disease   * Diabetic retinopathy * Diabetic kidney disease | 449(26%)  420(25%) | 216(22%)  156(16%) | 233(33%)  264(39%) |
| Macrovascular disease   * Ischemic heart disease/Heart failure * TIA/Stroke * Peripheral artery disease | 560(41%)  295(16%)  246(14%) | 0  0  0 | 560(73%)  295(37%)  246(32%) |
| CKD | NA | NA | NA |
| Death (in-hospital mortality) | 715(39%) | 326(31%) | 389(48%) |
| Length of hospital stay | NA | NA | NA |
| ICU admission | 193(10%) | 155(15%) | 38(5%) |
|  |  |  |  |

**Multivariable analysis on subgroup with complete data for all variables**

**Primary outcome**

* Death ~ Macrovascular disease (unadjusted)

Coefficients:

Estimate Std. Error z value Pr(>|z|)

(Intercept) -0.78678 0.06681 -11.78 < 2e-16 \*\*\*

MacrovascularD 0.72208 0.09718 7.43 1.08e-13 \*\*\*

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Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**OR 2.5 % 97.5 %**

**MacrovascularD 2.06 1.7 2.49**

* Death ~ Macrovascular disease + Age + Sex

Coefficients:

Estimate Std. Error z value Pr(>|z|)

(Intercept) -3.542150 0.319618 -11.082 < 2e-16 \*\*\*

MacrovascularD 0.472713 0.102038 4.633 3.61e-06 \*\*\*

Sex1 0.231646 0.103471 2.239 0.0252 \*

Age.At.Admission 0.037032 0.004165 8.890 < 2e-16 \*\*\*

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Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**OR 2.5 % 97.5 %**

**MacrovascularD 1.60 1.31 1.96**

**Sex1 1.26 1.03 1.54**

**Age.At.Admission 1.04 1.03 1.05**

* Death ~ Macrovascular disease + Age + Sex + Ethnic group + Type of Diabetes + BMI + Hypertension + Dyslipidaemia + Microvascular disease

Coefficients:

Estimate Std. Error z value Pr(>|z|)

(Intercept) -3.291842 0.488583 -6.738 1.61e-11 \*\*\*

MacrovascularD 0.444231 0.105994 4.191 2.78e-05 \*\*\*

Sex1 0.235847 0.105251 2.241 0.0250 \*

Age.At.Admission 0.040063 0.004627 8.659 < 2e-16 \*\*\*

Type.Of.Diabetes2 -0.355450 0.245292 -1.449 0.1473

BMI -0.002706 0.007600 -0.356 0.7218

Eth\_groupAsian 0.363973 0.153572 2.370 0.0178 \*

Eth\_groupBlack 0.251796 0.209588 1.201 0.2296

Eth\_groupOther -0.159568 0.194962 -0.818 0.4131

Hypertension1 -0.261659 0.111887 -2.339 0.0194 \*

MicrovascularD 0.180458 0.103867 1.737 0.0823 .

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Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**OR 2.5 % 97.5 %**

**MacrovascularD 1.56 1.27 1.92 (yes vs no)**

**Sex1 1.27 1.03 1.56 (male vs female)**

**Age.At.Admission 1.04 1.03 1.05**

**Type.Of.Diabetes1 0.70 0.43 1.13 (type 2 vs type 1)**

**BMI 1.00 0.98 1.01**

**Eth\_groupAsian 1.44 1.07 1.94 (vs white)**

**Eth\_groupBlack 1.29 0.85 1.94 (vs white)**

**Eth\_groupOther 0.85 0.58 1.25 (vs white)**

**Hypertension1 0.77 0.62 0.96 (yes vs no)**

**MicrovascularD 1.20 0.98 1.47 (yes vs no)**

*PLEASE ADD MODEL OUTPUT HERE*

**Secondary outcomes**

* Length of hospital stay ~ Macrovascular disease
* Length of hospital stay ~ Macrovascular disease + Age + Sex

Length of hospital stay ~ Macrovascular disease + Age + Sex + Ethnic group + Type of Diabetes + BMI + Hypertension + Dyslipidaemia + Microvascular disease

*PLEASE ADD MODEL OUTPUT*

* ICU admission ~ Macrovascular disease

Coefficients:

Estimate Std. Error z value Pr(>|z|)

(Intercept) -1.74442 0.08706 -20.038 < 2e-16 \*\*\*

MacrovascularD -1.25918 0.18761 -6.712 1.92e-11 \*\*\*

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Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**OR 2.5 % 97.5 %**

**MacrovascularD 0.28 0.20 0.41**

* ICU admission ~ Macrovascular disease + Age + Sex

Coefficients:

Estimate Std. Error z value Pr(>|z|)

(Intercept) 2.136641 0.370003 5.775 7.71e-09 \*\*\*

MacrovascularD -0.791287 0.201896 -3.919 8.88e-05 \*\*\*

Sex1 0.710039 0.184475 3.849 0.000119 \*\*\*

Age.At.Admission -0.067400 0.005778 -11.665 < 2e-16 \*\*\*

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Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**OR 2.5 % 97.5 %**

**MacrovascularD 0.45 0.31 0.67**

**Sex1 2.03 1.42 2.92**

**Age.At.Admission 0.93 0.92 0.95**

* ICU admission ~ Macrovascular disease + Age + Sex + Ethnic group + Type of Diabetes + BMI + Hypertension + Dyslipidaemia + Microvascular disease

Coefficients:

Estimate Std. Error z value Pr(>|z|)

(Intercept) -0.423740 0.659381 -0.643 0.520463

MacrovascularD -0.615142 0.212492 -2.895 0.003793 \*\*

Sex1 0.842741 0.192892 4.369 1.25e-05 \*\*\*

Age.At.Admission -0.060751 0.006764 -8.982 < 2e-16 \*\*\*

Type.Of.Diabetes1 0.410912 0.385787 1.065 0.286819

BMI 0.036735 0.011983 3.066 0.002172 \*\*

Eth\_groupAsian 0.813477 0.219593 3.704 0.000212 \*\*\*

Eth\_groupBlack 1.077082 0.306014 3.520 0.000432 \*\*\*

Eth\_groupOther 1.064288 0.251023 4.240 2.24e-05 \*\*\*

Hypertension1 0.274674 0.200032 1.373 0.169707

MicrovascularD -0.396921 0.191820 -2.069 0.038524 \*

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Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**OR 2.5 % 97.5 %**

**MacrovascularD 0.54 0.36 0.82**

**Sex1 2.32 1.59 3.39**

**Age.At.Admission 0.94 0.93 0.95**

**Type.Of.Diabetes1 1.51 0.71 3.21**

**BMI 1.04 1.01 1.06**

**Eth\_groupAsian 2.26 1.47 3.47**

**Eth\_groupBlack 2.94 1.61 5.35**

**Eth\_groupOther 2.90 1.77 4.74**

**Hypertension1 1.32 0.89 1.95**

**MicrovascularD 0.67 0.46 0.98**

*PLEASE ADD MODEL OUTPUT*

* use of IMV on admission ~ Macrovascular disease
* use of IMV on admission ~ Macrovascular disease + Age + Sex
* use of IMV on admission ~ Macrovascular disease + Age + Sex + Ethnic group + Type of Diabetes + BMI + Hypertension + Dyslipidaemia + Microvascular disease

*PLEASE ADD MODEL OUTPUT*

*Could also consider combined outcome ie death or ICU, as below*

* Death/ ICU admission ~ Macrovascular disease

Coefficients:

Estimate Std. Error z value Pr(>|z|)

(Intercept) -0.36881 0.06301 -5.853 4.83e-09 \*\*\*

MacrovascularD 0.42853 0.09461 4.530 5.91e-06 \*\*\*

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Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**OR 2.5 % 97.5 %**

**MacrovascularD 1.53 1.28 1.85**

* Death/ ICU admission ~ Macrovascular disease + Age + Sex

Coefficients:

Estimate Std. Error z value Pr(>|z|)

(Intercept) -1.195589 0.267379 -4.472 7.77e-06 \*\*\*

MacrovascularD 0.338804 0.098753 3.431 0.000602 \*\*\*

Sex1 0.302999 0.097872 3.096 0.001962 \*\*

Age.At.Admission 0.009335 0.003592 2.599 0.009346 \*\*

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Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**OR 2.5 % 97.5 %**

**MacrovascularD 1.40 1.16 1.70**

**Sex1 1.35 1.12 1.64**

**Age.At.Admission 1.01 1.00 1.02**

* Death/ ICU admission ~ Macrovascular disease + Age + Sex + Ethnic group + Type of Diabetes + BMI + Hypertension + Dyslipidaemia + Microvascular disease

Coefficients:

Estimate Std. Error z value Pr(>|z|)

(Intercept) -1.339768 0.432700 -3.096 0.001960 \*\*

MacrovascularD 0.358596 0.102798 3.488 0.000486 \*\*\*

Sex1 0.325306 0.099686 3.263 0.001101 \*\*

Age.At.Admission 0.014555 0.004091 3.558 0.000374 \*\*\*

Type.Of.Diabetes1 -0.316932 0.227455 -1.393 0.163503

BMI 0.001238 0.007121 0.174 0.861934

Eth\_groupAsian 0.472229 0.144132 3.276 0.001052 \*\*

Eth\_groupBlack 0.482067 0.200106 2.409 0.015994 \*

Eth\_groupOther 0.228908 0.174461 1.312 0.189492

Hypertension1 -0.202407 0.106362 -1.903 0.057039 .

MicrovascularD 0.061034 0.099818 0.611 0.540904

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Signif. codes: 0 ‘\*\*\*’ 0.001 ‘\*\*’ 0.01 ‘\*’ 0.05 ‘.’ 0.1 ‘ ’ 1

**OR 2.5 % 97.5 %**

**MacrovascularD 1.43 1.17 1.75**

**Sex1 1.38 1.14 1.68**

**Age.At.Admission 1.01 1.01 1.02**

**Type.Of.Diabetes1 0.73 0.47 1.14**

**BMI 1.00 0.99 1.02**

**Eth\_groupAsian 1.60 1.21 2.13**

**Eth\_groupBlack 1.62 1.09 2.40**

**Eth\_groupOther 1.26 0.89 1.77**

**Hypertension1 0.82 0.66 1.01**

**MicrovascularD 1.06 0.87 1.29**