**Supplementary Table 1.** $F_1$ scores of different combinations of bin sizes and ML algorithms. The combination of 10-Da bins and Light Gradient Boosting Machine has highest performance in the CMUH training dataset.

| F1 Score   | Bin Size (Da) | LightGBM | Gradient Boosting | Logistic Regression | Extreme Gradient Boosting | Extra Trees | Random Forest | Linear SVM | Decision Tree | K Neighbors | Naive Bayes |
|------------|---------------|----------|-------------------|---------------------|--------------------------|-------------|---------------|------------|---------------|------------|-------------|
| ML Algorithms | 1      | 5       | 10     | 15      | 20       | 0.8131     | 0.7985     | 0.8036     | 0.7943     | 0.7688     | 0.7629     | 0.7728     | 0.7294     | 0.6802     | 0.6775     | 0.8121     | 0.7962     | 0.7971     | 0.8045     | 0.8048     | 0.7583     | 0.7891     | 0.7264     | 0.7001     | 0.6793     | 0.6770     | 0.6782     | 0.6783     |
Supplementary Figure 1. Observations of the molecular feature at 6590–6599 Da in (a) year 2018 (b) year 2019 (c) year 2020 (d) year 2021
Supplementary Figure 2. The peak of m/z = 6593.2 in the MRSA strain was identified as UPF0337 protein SACOL1680. (a) The sequence of peptides separately identified in trypsin and Glu-C digestion was underlined and bolded. (b) The fragmented ion spectra of a peptide sequence of $^{31}$GQQDKVIGKAKEVVE$^{45}$. 
Supplementary Table 2. The identified peptide sequence of UPF0337 protein SACOL1680 and UPF0337 protein SA1452 by Trypsin and Glu-C.

enzyme digestion and nanoLC-MS/MS analysis.

| Sequence                      | Range | Scores | m/z meas. | Mr calc. | MH+ meas. | Rt [min] | Δ m/z [ppm] | Modifications |
|-------------------------------|-------|--------|-----------|----------|-----------|----------|-------------|---------------|
| UPF0337 protein SAUSA300      |       |        |           |          |           |          |             |               |
| (MRSA_Fraction 7_Trypsin)    |       |        |           |          |           |          |             |               |
| K.AKEVVENAK.N                | 40-48 | 34.6   | 494.261   | 986.5397 | 987.5147  | 13.18    | -32.59      |               |
| K.ITDAIDKLK.K                | 51-59 | 38.0   | 508.789   | 1015.5914| 1016.5707 | 15.36    | -27.45      |               |
| K.NKJTDAIDK.L                | 49-57 | 49.6   | 509.2692  | 1016.5502| 1017.5312 | 14.19    | -25.82      |               |
| K.ITDAIDKLKK.-               | 51-60 | 51.0   | 572.8394  | 1143.6863| 1144.6715 | 13.65    | -19.25      |               |
| M.ADESKFDQFK.G               | 2-11  | 89.7   | 607.7707  | 1213.5615| 1214.5341 | 15.32    | -28.54      |               |
| K.AKEVVENAKNK.I              | 40-50 | 56.2   | 615.3261  | 1228.6776| 1229.645  | 11.01    | -32.39      |               |
| K.NKJTDAIDK.L                | 49-59 | 60.9   | 629.854   | 1257.7293| 1258.7008 | 21.62    | -28.38      |               |
| K.ETVGNVTDNKE.LEK.E          | 16-29 | 121.8  | 788.3759  | 1574.7788| 1575.7444 | 13.91    | -26.39      |               |
| M.ADESKFDQFKGNVK.E           | 2-15  | 121.2  | 806.8778  | 1611.7893| 1612.7483 | 14.74    | -29.89      |               |
| K.EVVENAKNKJTDAIDK.L         | 42-57 | 143.6  | 893.955   | 1785.9472| 1786.9027 | 18.83    | -29         |               |
| UPF0337 protein SAUSA300      |       |        |           |          |           |          |             |               |
| (MRSA_Fraction 7_Glu-C)      |       |        |           |          |           |          |             |               |
| E.TVGNVTDNKE.L               | 17-26 | 63.6   | 538.7546  | 1075.5146| 1076.5019 | 13.25    | -18.47      |               |
| E.NAKNKJTDAIDKLLK.-          | 46-60 | 131.6  | 567.3288  | 1698.9992| 1699.9719 | 15.07    | -20.3       |               |
| E.NAKNKJTDAIDKLLK.-          | 46-60 | 152.7  | 567.6577  | 1699.9832| 1700.9584 | 18.62    | -18.86      | Deamidated: 1 |
| E.NAKNKJTDAIDKLLK.-          | 46-60 | 122.7  | 567.6578  | 1699.9832| 1700.9588 | 17.07    | -18.59      | Deamidated: 4 |
| D.KVIGKAKEVVE.N              | 35-45 | 35.2   | 600.3589  | 1198.7285| 1199.7105 | 12.79    | -21.1       |               |
| Sequence                            | Start - End | p.m. | M.W. (Da) | Xcorr. | Delta (ppm) |
|-------------------------------------|-------------|------|-----------|--------|-------------|
| E.QQDKVIGKAKE.V                     | 31 - 42     | 88.5 | 650.8508  | 1299.7147 | 7.63        |
| E.TVGNVTDNKELE.K                    | 17 - 28     | 61.3 | 659.8144  | 1317.6412 | 15.34       |
| E.SKFDQFKGNVKE.T                    | 5 - 16      | 71.9 | 713.8551  | 1425.7252 | 13.37       |
| E.KEQQDKVIGKAKE.V                   | 29 - 42     | 59.9 | 779.4154  | 1556.8522 | 8.86        |
| E.QQDKVIGKAKEVVE.N                  | 31 - 45     | 99.1 | 814.4373  | 1627.8674 | 14.58       |
| K.ITDAIDKLK.K                       | 51 - 59     | 34.6 | 508.7906  | 1015.5914 | 15.48       |
| K.NKITDAIDK.L                       | 49 - 57     | 48.8 | 509.2681  | 1016.5502 | 14.13       |
| K.ITDAIDKLKK.K                      | 51 - 60     | 42.0 | 572.8364  | 1143.6863 | 13.59       |
| M.ADESQFDQFK.G                      | 2 - 11      | 89.8 | 607.7706  | 1213.5615 | 15.44       |
| K.NKITDAIDK.K                       | 49 - 59     | 44.2 | 629.8538  | 1257.7293 | 21.66       |
| K.ETVGNVTDNKELE.K                   | 16 - 29     | 121.5| 788.3747  | 1574.7788 | 13.93       |
| K.ETVGNVTDNKELE.E                   | 16 - 29     | 31.0 | 788.8777  | 1575.7421 | 13.88       |
| M.ADESQFDQFKGNVE.K                  | 2 - 15      | 116.9| 806.8795  | 1611.7893 | 14.28       |
| K.EVVENAKNKTDAIDK.L                 | 42 - 57     | 136.5| 596.3058  | 1785.9472 | 18.99       |

**UPF0337 protein SA1452**

(MSSA_Fraction 5_Trypsin)

| Sequence                            | Start - End |
|-------------------------------------|-------------|
| K.ETVGNVTDNKELE.K                   | 17 - 28     |
| E.SKFDQFKGNVKE.T                    | 5 - 16      |
| D.ESKFDQFKGNVKE.T                   | 4 - 16      |
| E.QQDKKATGKAKEVVE.N                 | 31 - 45     |

**UPF0337 protein SA1452**

(MSSA_Fraction 5_Glu-C)

| Sequence                            | Start - End | p.m. | M.W. (Da) | Xcorr. | Delta (ppm) |
|-------------------------------------|-------------|------|-----------|--------|-------------|
| E.TVGNVTDNKELE.K                    | 17 - 28     | 52.6 | 659.8147  | 1317.6412 | 16.04       |
| E.SKFDQFKGNVKE.T                    | 5 - 16      | 72.7 | 713.8469  | 1425.7252 | 14.61       |
| D.ESKFDQFKGNVKE.T                   | 4 - 16      | 78.0 | 778.367   | 1554.7678 | 14.57       |
| E.QQDKKATGKAKEVVE.N                 | 31 - 45     | 31.7 | 794.3926  | 1586.8264 | 6.74        |
| Sequence                  | Start - End | m/z     | p/µL | Precursor | Charge | m/z Calculated | Mass Error | Deamidation |
|---------------------------|-------------|---------|------|-----------|--------|----------------|------------|-------------|
| E.NAKNKITDAIDKLKK.        | 46 - 60     | 46      | 112.7| 850.4794  | 14.6   | 1698.9992      | 1699.9515  | 14.96       | -32.32      |
| E.NAKNKITDAIDKLKK.        | 46 - 60     | 86.6    | 850.9701 | 1699.9832 | 17.57  | 1700.9329      | 1700.9392  | 17.57       | -33.85      |
| E.NAKNKITDAIDKLKK.        | 46 - 60     | 112.8   | 567.6513 | 1699.9832 | 18.49  | 1700.9392      | 1700.9392  | 18.49       | -30.13      |