

MULTIMARKER RISK STRATIFICATION

CLAIM OF PRIORITY

This application claims priority to U.S. Provisional Patent Application Serial No. 61/691,706, filed on August 21, 2012. The entire contents of the foregoing are incorporated by reference herein.

TECHNICAL FIELD

The invention relates to methods for predicting risk of mortality, in subjects with cardiovascular disease, e.g., heart failure, based on multiple markers including a combination of biomarkers (e.g., ST2) and other clinical parameters (e.g., age).

BACKGROUND

Clinical evaluation for determination of risk of mortality due to heart failure may not always be straightforward. The decision whether to treat a subject aggressively or conservatively, or to admit the subject as an inpatient or to send them home, may sometimes be made solely on a physician's clinical assessment or "gut feeling" as to the individual's actual condition. A formula for determining a subject's likelihood of mortality would significantly enhance the physician's ability to make informed treatment decisions, improve patient care and reduce overall healthcare costs. A multi-marker approach for risk stratification has been generally proposed for patients with acute coronary syndromes, see, e.g., Sabatine et al., *Circulation* 105(15):1760-3 (2002)), and methods for predicting risk of a major adverse cardiac event are describe in U.S. Patent No. 8090562.

SUMMARY

The present ~~invention~~-disclosure is based, at least in part, on the discovery that multiple markers, including serum levels of the biomarker ST2 (also known as Interleukin 1 Receptor Like 1 (IL1RL-1)), in combination with clinical parameters such as age and levels of at least one other biomarker, e.g., troponin or a natriuretic peptide (NP) such as the inactive N-terminal fragment of brain-type natriuretic peptide (NT-pro-BNP), can be used predict the likelihood of mortality due to CVD within a specific time period, e.g., 30 days, 3 or 6 months, or a year or more (e.g., 2, 5 or 10 years).

cardiovascular disorder that include determining the subject's risk of mortality over a specific time period (e.g., within any of the time periods described herein, e.g., within 3 months, 6 months, 1, 2, 5 or 10 years) using any of the methods described herein, and selecting continuation of the treatment for a subject determined to have a reduced risk of mortality over the specific time period (e.g., using any of the methods described herein) or selecting a new (alternate) cardiovascular treatment for a subject determined to have an increased risk of mortality over the specific time period (e.g., using any of the methods described herein). In one aspect, there is provided an in vitro method for selecting a treatment for a subject receiving a treatment for a cardiovascular disorder, wherein the method comprises:

determining a multimarker mortality risk score using one of the following algorithms:

(1) the age of the subject (AGE) + the level of soluble ST2 in a biological sample from the subject (ST2) + a natural logarithm of a systolic blood pressure (ln_SBP) + a history of cardiovascular disease (CAD) + a natural logarithm of a level of a brain natriuretic peptide (BNP) in the subject (ln_NTpro-BNP)

(2) AGE + ST2 + ln_NTpro-BNP

(3) AGE + ST2 + a level of troponin in the subject (Troponin) + a New York Heart Association (NYHA) score (NYHA)

(4) AGE + ST2 + [Troponin or NYHA]

(5) AGE + ST2 + [Troponin and/or NYHA] + a natural logarithm of a level of hemoglobin (ln_Hgb)

(6) AGE + ST2 + [Troponin and/or NYHA] + ln_Hgb + ln_SBP

(7) AGE + ST2 + [Troponin and/or NYHA] + ln_Hgb + ln_NTpro-BNP;

comparing the multimarker mortality risk score to a reference multimarker mortality risk score; and

selecting an alternate cardiovascular treatment for a subject having a multimarker mortality risk score that is elevated as compared to the reference multimarker mortality score, or

selecting continuation of the cardiovascular treatment previously administered for a subject having a multimarker mortality risk score that is decreased as compared to the reference multimarker mortality risk score. As described herein, a new treatment can mean administration of a new combination therapeutic agents, administration of a new therapeutic agent, a different dosage of the previously administered therapeutic agent, a different frequency of administration of the previously administered therapeutic agent, or a different route of administration of the previously administered therapeutic agent. Some embodiments further include administering the selected treatment to a subject.

Also provided are methods of selecting a subject for a clinical study that include determining a subject's risk of mortality within a specific time period (e.g., any of the specific time periods described herein, e.g., within 3 months, 6 months, 1, 2, 5 or 10 years) (e.g., using any of the methods described herein) and selecting a subject determined to have an increased risk of mortality within the specific time period for participation in a clinical study.

Also provided herein are methods of determining whether a subject's risk of mortality (e.g., caused by a cardiovascular disorder) is increasing or decreasing over time. These methods include determining a first multimarker mortality risk score in a subject at a first time point (e.g., using any of the methods described herein), determining a second multimarker risk score in a subject at a second time point (e.g., using any of the methods described herein), comparing the second multimarker risk score to the first multimarker risk score, and identifying a subject having an elevated second multimarker risk score as compared to the first multimarker risk score as having an increasing risk of mortality over time or identifying a subject having a decreased second multimarker risk score as compared to the first multimarker risk score as having a decreasing risk of mortality over time.

Also provided are methods of determining the efficacy of a treatment for a cardiovascular disorder (e.g., heart failure) in a subject that include, determining a

second time point (e.g., using any of the methods described herein), and selecting a subject having an elevated second multimarker risk score as compared to first multimarker risk score for participation in a clinical study of a cardiovascular disease.

As used herein, a “sample” includes any bodily fluid or tissue, e.g., one or more of blood, serum, plasma, urine, and body tissue. In certain embodiments, a sample is a serum, plasma, or blood sample.

An antibody that “binds specifically to” an antigen, binds preferentially to the antigen in a sample containing other proteins.

The methods and kits described herein have a number of advantages. For example, the methods can be used to determine whether a patient should be admitted or held as an inpatient for further assessment, regardless of whether a definitive diagnosis has been made. For example, the methods can be used for risk stratification of a given subject, e.g., to make decisions regarding the level of aggressiveness of treatment that is appropriate for the subject, based on their multimarker risk score as determined by a method described herein. Better treatment decisions can lead to reduced morbidity and mortality, and better allocation of scarce health care resources. The methods described herein can be used to make general assessments as to whether a patient should be further tested to determine a specific diagnosis. The methods described herein can also be used for patient population risk stratification, e.g., to provide information about clinical performance or expected response to a therapeutic intervention. The methods described herein can be used regardless of the underlying cause or ultimate diagnosis, and therefore are not limited to specific indications.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this ~~invention-disclosure~~ belongs. Methods and materials are described herein for use in the present ~~invention-disclosure~~; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting.

All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In addition, the present application incorporates by reference the entire contents of U.S. Patent Application No. 11/789,169, and international patent application nos. PCT/US2007/067626, PCT/US2007/067914, and PCT/US2007/068024.

In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the ~~invention-disclosure~~ will be apparent from the following detailed description and Figures, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1 shows the summary statistics for individual variables for 1 year-mortality.

Figure 2 shows the summary statistics for individual variables for 5-year mortality.

Figures 3-24 show linearity checks and cut-point evaluations performed for each variable.

Figures 25 and 26 provide a summary of the results for each variable.

Figures 27-34 show the results of several heuristic approaches used to identify the best models for predicting risk of death, including backward, forward, and stepwise selection. Selection in each instance was made based on AIC (Akaike's Information Criteria) or BIC (Bayesian Information Criteria).

Figure 35 shows the co-linearity analysis of several variables with risk of death.

Figure 36 is a summary of the univariate performance of each variable.

Figures 37-49 show the results of linearity checks performed for each variable.

Figure 50 provides a summary of the results for each variable.

Figure 51 shows AIC-based marker selection.

Figure 52 shows BIC-based marker selection.

Figure 53 and 54 show a comparison of two models ($[Age + Ln_SBP + CAD + ST2 \geq 35 + LN_NTBNP]$ and $[Age + ST2 \geq 35 + LN_NTBNP]$).

Figure 55 shows bootstrap AUC estimates for the 5-parameter and the 3-parameter model.

Figure 56 is a graph showing the model calibration for the 5-parameter and the 3-parameter model.

Figure 57 is list of exemplary model parameters.

DETAILED DESCRIPTION

Clinical evaluation of patients, particularly patients with non-specific symptoms such as dyspnea or chest pain, is often challenging. The results described

WHAT IS CLAIMED IS:

1. A method for evaluating the risk of mortality for a subject within one year, the method comprising:

determining a multimarker mortality risk score for a subject based upon:

the age of the subject;

the level of ST2 in the subject, in combination with one or more of a natural logarithm of a level of a brain natriuretic peptide (BNP) in the subject; a level of troponin in the subject; a New York Heart Association (NYHA) score; a history of cardiovascular disease (CAD); a natural logarithm of a systolic blood pressure; a measure of renal function or a natural logarithm of a level of hemoglobin (Hgb), age; and

comparing the multimarker mortality risk score to a reference multimarker mortality risk score;

wherein the presence of a multimarker mortality risk score that is at or above the reference multimarker mortality risk score indicates that the subject has an increased risk of mortality within one year.

2. The method of claim 1, wherein the risk score is determined using one of the following algorithms:

(9) $AGE + ST2 + \ln_SBP + CAD + \ln_NTpro\text{-}BNP$

(10) $AGE + ST2 + \ln_NTpro\text{-}BNP$

(11) $AGE + ST2 + Troponin + NYHA$

(12) $AGE + ST2 + [Troponin \text{ OR } NYHA]$

(13) $AGE + ST2 + [Troponin \text{ AND/OR } NYHA] + \ln_Hgb$

(14) $AGE + ST2 + [Troponin \text{ AND/OR } NYHA] + \ln_Hgb$

(15) $AGE + ST2 + [Troponin \text{ AND/OR } NYHA] + \ln_Hgb + \ln_SBP$

(16) $AGE + ST2 + [Troponin \text{ AND/OR } NYHA] + \ln_Hgb + \ln_SBP + \ln_NTpro\text{-}BNP$

3. The method of claim 2, wherein the level of ST2 is determined and compared to a threshold and the presence of a level at or above the threshold is scored as "1" and the presence of a level below the threshold is scored as "0".

4. The method of claim 3, wherein the threshold is 35 or 50 ng/mL.

5. The method of claim 4, wherein algorithm (1) or (2) is used and the threshold level of ST2 is 35 ng/ml.

6. The method of claim 4, wherein algorithm (3) or (4) is used and the threshold level of ST2 is 50 ng/ml.

7. The method of claim 1, wherein the subject has been diagnosed with heart failure.

8. The method of claim 1, wherein the reference multimarker mortality risk score represents a score corresponding to a low risk of death within one year or within five years.

9. The method of claim 1, wherein the sample comprises serum, blood, plasma, urine, or body tissue.

10. The method of claim 1, wherein the subject has a BMI of 25-29, a BMI of ≥ 30 , or renal insufficiency.

11. The method of claim 1, further comprising discharging the subject or treating the subject on an inpatient basis based on the presence of an increased risk of mortality.

WHAT IS CLAIMED IS:

1. An in vitro method for selecting a treatment for a subject receiving a treatment for a cardiovascular disorder, wherein the method comprises:

determining a multimarker mortality risk score using one of the following algorithms:

(1) the age of the subject (AGE) + the level of soluble ST2 in a biological sample from the subject (ST2) + a natural logarithm of a systolic blood pressure (ln_SBP) + a history of cardiovascular disease (CAD) + a natural logarithm of a level of a brain natriuretic peptide (BNP) in the subject (ln_NTpro-BNP)

(2) AGE + ST2 + ln_NTpro-BNP

(3) AGE + ST2 + a level of troponin in the subject (Troponin) + a New York Heart Association (NYHA) score (NYHA)

(4) AGE + ST2 + [Troponin or NYHA]

(5) AGE + ST2 + [Troponin and/or NYHA] + a natural logarithm of a level of hemoglobin (ln_Hgb)

(6) AGE + ST2 + [Troponin and/or NYHA] + ln_Hgb + ln_SBP

(7) AGE + ST2 + [Troponin and/or NYHA] + ln_Hgb + ln_NTpro-BNP;

comparing the multimarker mortality risk score to a reference multimarker mortality risk score; and

selecting an alternate cardiovascular treatment for a subject having a multimarker mortality risk score that is elevated as compared to the reference multimarker mortality score, or

selecting continuation of the cardiovascular treatment previously administered for a subject having a multimarker mortality risk score that is decreased as compared to the reference multimarker mortality risk score.

2. The method of claim 1, wherein the level of soluble ST2 is determined and compared to a threshold and the presence of a level at or above the threshold is scored as "1" and the presence of a level below the threshold is scored as "0".

3. The method of claim 2, wherein the threshold is 35 or 50 ng/mL.

4. The method of claim 3, wherein the algorithm (1) or (2) is used and the threshold level of soluble ST2 is 35 ng/mL.

5. The method of claim 3, wherein algorithm (3) or (4) is used and the threshold level of soluble ST2 is 50 ng/mL.

6. The method of claim 1, wherein the subject has been diagnosed with heart failure.

7. The method of claim 1, wherein the reference multimarker mortality risk score represents a score corresponding to a low risk of death within one year or within five years.

8. The method of claim 1, wherein the reference multimarker mortality risk score represents a threshold level.

9. The method of claim 1, wherein the sample comprises blood, serum, or plasma.

10. The method of claim 1, wherein the subject has a BMI of 25-29.

11. The method of claim 1, wherein the subject has a BMI of ≥ 30 .

12. The method of claim 1, wherein the subject has renal insufficiency.