

## Prognostic Significance of Hemoglobin Levels in Patients With Heart Failure

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**Introduction and objectives.** To evaluate the prognostic significance of hemoglobin (Hb) levels in terms of 1-year mortality and hospital admissions due to heart failure (HF) during the first year of follow-up after the first visit to an outpatient HF unit.

**Patients and method.** Survival status and HF-related hospital admission rate at 1 year were analyzed for 337 patients admitted between August 2001 and March 2003. Plasma Hb level was measured at the first visit to the unit.

**Results.** 28 patients (8%) died and there were 158 HF-related hospital admissions in 66 patients. Plasma Hb level correlated strongly with survival at 1 year, and was  $13.0 \pm 1.7$  g/dL in patients who were alive after this time, versus  $11.7 \pm 1.6$  g/dL ( $P < .001$ ) in patients who died. Plasma Hb level also correlated with HF-related need for hospital admission, and was  $13.1 \pm 1.7$  g/dL in patients who were not hospitalized, versus  $12.2 \pm 1.7$  g/dL ( $P < .001$ ) in patients with at least 1 hospital admission. In the multivariate logistic regression analysis plasma Hb level remained statistically associated both with 1-year survival and with the need for HF-related hospital admission. On the basis of a cutoff value for anemia of  $Hb < 12$  g/dL, 30% of the patients had anemia. One-year mortality was 17% in patients with anemia and 5% in patients without anemia ( $P < .001$ ). Among patients without anemia, 31% had at least one HF-related hospital admission, whereas only a 15% of the patients without anemia needed to be hospitalized for HF ( $P = .001$ ).

**Conclusions.** Plasma Hb levels correlated inversely with mortality and with HF-related hospital admissions at 1 year. The prevalence of anemia ( $Hb < 12$  g/dL) in the population with HF studied here was high and had independent prognostic value.

**Key words:** Anemia. Hemoglobin. Heart failure. Survival.

### Significado pronóstico de los valores de hemoglobina en pacientes con insuficiencia cardíaca

**Introducción y objetivos.** Evaluar el valor pronóstico de las concentraciones de hemoglobina (Hb) en relación con la mortalidad y con los ingresos hospitalarios por insuficiencia cardíaca (IC) al año de la primera visita a la Unidad de IC.

**Pacientes y método.** Conocemos la situación vital y los ingresos por IC al año en 337 pacientes admitidos entre agosto de 2001 y marzo de 2003. Las concentraciones de Hb se recogieron en la primera visita.

**Resultados.** Fallecieron 28 (8%) pacientes y hubo 158 ingresos por IC en 66 pacientes. Los valores de Hb se asociaron con la mortalidad a 1 año (pacientes vivos,  $13,0 \pm 1,7$  g/dl; pacientes fallecidos,  $11,6 \pm 1,7$  g/dl;  $p < 0,001$ ) y con la necesidad de ingresar por IC (pacientes sin ingresos,  $13,1 \pm 1,7$  g/dl; pacientes con al menos un ingreso,  $12,2 \pm 1,7$  g/dl;  $p < 0,001$ ). En el análisis multivariable, los valores de Hb mantuvieron la significación estadística. Definida la anemia como  $Hb < 12$  g/dl, el 30% de los pacientes estaba anémico. La mortalidad al año fue del 17% en los pacientes anémicos y del 5% en el grupo sin anemia ( $p < 0,001$ ). El 31% de los pacientes con anemia tuvo al menos un ingreso hospitalario por IC, mientras que sólo el 15% de los pacientes no anémicos precisó ingresar ( $p = 0,001$ ).

**Conclusiones.** Los valores de Hb se asocian inversamente con la mortalidad y los ingresos por IC en el primer año de seguimiento. La prevalencia de anemia en nuestra población con IC es elevada y tiene valor pronóstico independiente.

**Palabras clave:** Anemia. Hemoglobina. Insuficiencia cardíaca. Supervivencia.

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Received April 21, 2004.

Accepted for publication October 26, 2004.

## INTRODUCTION

Anemia is frequent in patients with heart failure (HF) and prevalence is in the 5%-55% range depending on the criteria used and population studied.<sup>1</sup> Degree of anemia correlates with seriousness of HF<sup>2-6</sup> and

## ABBREVIATIONS

Hb: hemoglobin.

HF: heart failure.

ACE inhibitors: angiotensin converting enzyme inhibitors.

prognosis.<sup>4-10</sup> Anemia in patients with HF is probably multifactorial and may be due to reduced intestinal iron absorption,<sup>11-14</sup> increased cytokine production of tumor necrosis factor alpha in particular which causes bone marrow depression, renin-angiotensin-aldosterone system activation causing sodium and water retention with dilutional anemia, renal insufficiency that frequently affects patients with HF (partly due to vasoconstriction and renal ischemia) and entails reduced erythropoietin production, loss of erythropoietin and of transferrin due to the coexistence of proteinuria, angiotensin converting enzyme (ACE) inhibitor treatment which, especially at high dosage, can influence erythropoietin production in the kidney and bone marrow response to this, antiplatelet agents or anticoagulants which can contribute to the presence of anemia and cause blood loss. Moreover, anemia itself contributes to HF requiring increased cardiac output to deliver oxygen to the tissues, which produces sympathetic stimulation with vasoconstriction and tachycardia. Renal vasoconstriction activates the renin-angiotensin-aldosterone system with reduced renal flow and water retention leading to secondary kidney failure that worsens anemia and, in the long-term, causes hypertrophy and ventricular remodeling that aggravates HF.

Awareness of the high prevalence of anemia in the population attending our HF Unit<sup>15</sup> led us to evaluate the prognostic significance of plasma hemoglobin (Hb) levels in terms of mortality and HF-related admissions at 1 year follow-up.

## PATIENTS AND METHODS

In our multidisciplinary HF unit, we prospectively gathered first visit Hb level data on all patients together with other demographic, clinical, biochemical, and therapeutic parameters. We then determined the prevalence of anemia, defined *a priori* as Hb<12 g/dL, which is considered the lower limit of normal in adult males and post-menopausal women.<sup>16</sup> In a cross-sectional study, we correlated Hb levels with various parameters.<sup>15</sup> Patients with the criterion of admission for HF as their principal problem were referred to the HF unit from the hospital Cardiology and Internal Medicine services and, to a lesser extent, from Emergency Room, other hospital services and outpatient cardiologists in the area. At 1 year, we correlated plasma Hb le-

vels with mortality and HF-related admission in 337 patients. We also analyzed mortality and HF-related admission in terms of presence or absence of anemia (Hb<12 mg/dL).

Statistical analysis was performed with SPSS for Windows 11.0. We considered  $P<.05$  statistically significant. Correlations of Hb levels (with a normal distribution) and continuous variables were analyzed by linear regression and associations with dichotomous parameters by the Student *t* test. In univariate analysis of Hb level association with different parameters, statistical significance was adjusted with Bonferroni correction. Univariate analysis of associations between Hb levels and mortality or HF-related admission was by the Student *t* test. Subsequently, to adjust Hb levels for clinical parameters, we performed multivariate logistic regression analysis using the forward stepwise method and including 1-year mortality and HF-related admission as dependent variables in addition to the independent variables listed in Table 1. We also used logistic regression analysis to calculate the odds ratio (OR) of the variable anemia.

The study was carried out fulfilling the personal data protection law and in agreement with the international recommendations for clinical research of the World Medical Association Declaration of Helsinki.

## RESULTS

Between August 2001 and March 2003, 341 patients were admitted to the HF unit. Survival status and incidence of HF-related admission at 1 year follow-up are known for 337 of these patients (72% men; mean age,  $65.4\pm 10$  years). Demographic characteristics appear in Table 2. Table 3 shows correlations between Hb level and various parameters with initial statistical significance and statistical significance adjusted with Bonferroni correction. Given our definition of anemia, this was present in 30% of patients. The relationship between prevalence of anemia and NYHA (New York Heart Association) functional class is clear (Figure 1).

During the first year of follow-up, 28 (8%) of the 337 patients died and 158 HF-related hospitalizations were recorded in 66 patients (Table 4). Hemoglobin

TABLE 1. Variables Introduced in Logistic Regression Models\*

|                         |
|-------------------------|
| Age                     |
| Gender                  |
| Diabetes                |
| AHT                     |
| Hemoglobin levels       |
| ACE inhibitor treatment |
| Beta-blocker treatment  |

\*AHT indicates arterial hypertension; ACE inhibitors, angiotensin converting enzyme inhibitors.

levels correlated significantly with 1-year mortality (patients who were alive  $13 \pm 1.7$  g/dL, patients who died  $11.6 \pm 1.7$  g/dL;  $P < .001$ ) (Figure 2). We also found significant correlations with HF-related admission (patients without admissions  $13.1 \pm 1.7$  g/dL, patients with  $\geq 1$  admissions  $12.2 \pm 1.7$  g/dL;  $P < .001$ ). In the logistic regression analysis, Hb levels remained in the model and maintained statistical significance in terms of 1-year mortality (OR=0.60; 95% CI, 0.46-0.79;  $P < .001$ ) and HF-related admission (OR=0.79; 95% CI, 0.66-0.95;  $P = .013$ ). Given our definition of anemia as Hb<12 g/dL, anemia was present in 30% of patients. One-year mortality was 17% in patients with anemia and 5% in those without ( $P < .001$ ) (Figure 3). Risk of death during the first year of follow-up was  $\geq 3$  times greater in patients with anemia (OR=3.5; 95% CI, 1.62-7.86;  $P = .002$ ). Figure 4 shows Kaplan-Meier survival curves for patients with and without anemia. Some 31% of patients with anemia had  $\geq 1$  HF-related hospitalization versus 15% of patients without anemia ( $P = .001$ ). Risk of HF-admission during the first year of follow-up was  $\geq 2$  times greater in patients with anemia (OR=2.3; 95% CI, 1.37-4.17;  $P = .002$ ).

## DISCUSSION

Anemia is present in 5%-55% of patients with HF depending on selection criteria and on the definition of anemia used.<sup>1</sup> In our series, which corresponds to the general population attended in a multidisciplinary HF Unit of a tertiary hospital without a transplant program, prevalence of anemia (defined as Hb<12 g/dL) is approximately in the center of this range. Anemia in HF is multifactorial. One of the most widely published series (12 065 patients) reported 58% of patients presented anemia of chronic disease.<sup>4</sup> In a much smaller series (37 patients) that analyzed data on hemodilution, this was the cause of anemia in 46% of patients.<sup>6</sup> Our series did not include data on hemodilution. One highly significant aspect of our population is the clear relationship between presence of anemia and NYHA functional class. This relationship is described by other authors<sup>2,5,6</sup> although in some series<sup>3</sup> Hb levels vary little when comparing functional classes and significant differences are found only by comparing classes I and II with classes III and IV. The relationship between Hb levels and HF-related admissions in the previous year is also highly significant, a phenomenon also observed by Felker et al.<sup>9</sup> Another significant finding is the relationship seen in our population between lower Hb levels and the coexistence of diabetes, a phenomenon observed by some authors<sup>9</sup> but not by others.<sup>3,5</sup> Ezekowitz et al.,<sup>4</sup> reporting a series including 12 065 patients, found a relationship between diabetes and anemia of chronic disease but not between diabetes and

TABLE 2. Baseline Characteristics\*

|                                       |               |
|---------------------------------------|---------------|
| Number of patients                    | 337           |
| Men/women                             | 244/93        |
| Age, years (mean $\pm$ SD)            | 65.4 $\pm$ 10 |
| Etiology                              |               |
| Ischemic heart disease                | 198 (59%)     |
| Dilated cardiomyopathy                | 38 (11%)      |
| Hypertensive cardiomyopathy           | 27 (8%)       |
| Alcoholic cardiomyopathy              | 21 (6%)       |
| Toxic cardiomyopathy                  | 4 (1%)        |
| Valvular heart disease                | 22 (7%)       |
| Other                                 | 27 (8%)       |
| Evolution, months (median)            | 26            |
| NYHA functional class                 |               |
| I                                     | 17 (5%)       |
| II                                    | 154 (46%)     |
| III                                   | 150 (44%)     |
| IV                                    | 16 (5%)       |
| Patient referrals from                |               |
| Cardiology                            | 90 (26%)      |
| Internal medicine                     | 40 (12%)      |
| Cardiology outpatients                | 164 (49%)     |
| Internal medicine outpatients         | 7 (2%)        |
| Other                                 | 36 (11%)      |
| Ejection fraction (mean $\pm$ SD)     | 31.6 $\pm$ 12 |
| Hemoglobin <12 g/dL                   | 100 (30%)     |
| Renal insufficiency (creatinine >2.5) | 20 (6%)       |
| Diabetes                              | 137 (41%)     |
| AHT                                   | 185 (55%)     |
| Previous AMI                          | 185 (55%)     |

\*SD indicates standard deviation; AHT, arterial hypertension; AMI, acute myocardial infarction; NYHA, New York Heart Association.

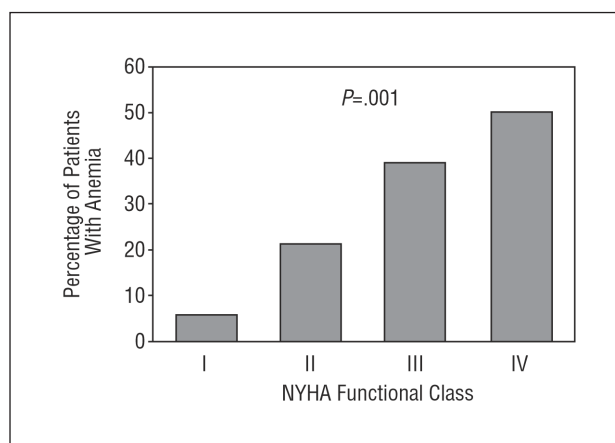


Figure 1. Percentage distribution of patients with anemia by functional class for heart failure (NYHA).

all anemia. In any case, our multivariate analysis showed the relationship between diabetes and Hb levels lost statistical significance. We were also surprised to see the relationship between plasma Hb levels and cholesterol (higher cholesterol levels associated with higher Hb levels). Horwich et al<sup>5</sup> also found similar data. The malnutrition that accompanies advanced

TABLE 3. Relationship Between Hemoglobin Levels and Various Demographic, Clinical, and Therapeutic Parameters\*

| Variables  | P Original (Without Adjustment) | P Adjusted With Bonferroni Correction | Degree of Association (95% CI) |
|--|---------------------------------|---------------------------------------|--------------------------------|
| <b>Demographics</b>                                  |                                 |                                       |                                |
| Age  | <0.001†                         | <0.001†                               | –0.049 (–0.067 to –0.033)      |
| Gender‡  | <0.001                          | <0.001                                | M, 13.28±1.7; W, 12.09±1.5     |
| Evolution period                                     | NS                              | NS                                    |                                |
| Etiology of cardiomyopathy                           | 0.003                           | NS                                    |                                |
| Diabetes mellitus\$                                  | <0.001                          | <0.001                                | D, 12.45±1.7; non-D, 13.26±1.7 |
| Arterial hypertension                                | NS                              | NS                                    |                                |
| Ejection fraction                                    | <0.05                           | NS                                    |                                |
| NYHA Functional class                                | <0.001†                         | <0.001†                               | –0.76 (–0.90 to –0.49)         |
| Number of HF-related admissions in the previous year | <0.001†                         | <0.001†                               | –0.13 (–0.23 a –0.031)         |
| Creatinine levels                                    | <0.001†                         | 0.001†                                | –0.52 (–0.77 to –0.27)         |
| Urea levels  | <0.001†                         | <0.001†                               | –0.011 (–0.015 to –0.007)      |
| Cholesterol levels                                   | <0.001\$                        | <0.001†                               | 0.016 (0.012–0.020)            |
| <b>Medication</b>                                    |                                 |                                       |                                |
| ACE inhibitors                                       | <0.05\$                         | NS                                    |                                |
| ARA-II   | NS                              | NS                                    |                                |
| Loop-acting diuretics                                | 0.006                           | NS                                    |                                |
| Beta-blockers  | 0.009II                         | NS                                    |                                |
| Digoxin  | NS                              | NS                                    |                                |
| Spironolactone                                       | NS                              | NS                                    |                                |
| Nitrates   | 0.01                            | NS                                    |                                |
| Anticoagulants                                       | NS                              | NS                                    |                                |
| Antiplatelet agents                                  | NS                              | NS                                    |                                |
| Statins  | NS                              | NS                                    |                                |

\*ARA-II indicates angiotensin II receptor antagonists; D, patients with diabetes; HF, heart failure; ACE inhibitors, angiotensin converting enzyme inhibitors; W, women; non-D: patients without diabetes; NS, not significant; NYHA, New York Heart Association; M, men.

†In older patients, with higher functional class, creatinine levels, urea levels and numbers of admissions in the previous year, corresponding to lower hemoglobin levels.

‡Gender and diabetes: levels in g/dL, mean ± standard deviation.

\$Higher levels of hemoglobin for higher levels of cholesterol.

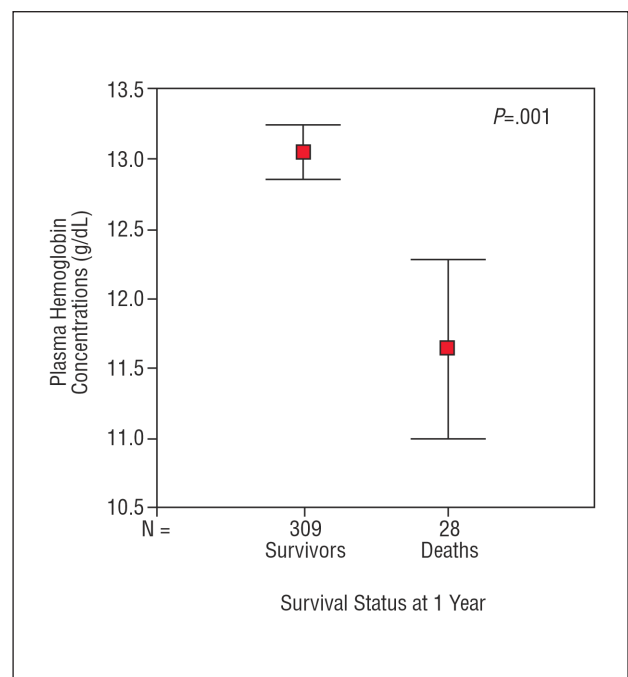
IIHigher levels of hemoglobin in those patients taking the drug.

TABLE 4. Survival Status at 1 Year and Number of Admissions for Heart Failure (HF) in the First Year of Follow-up

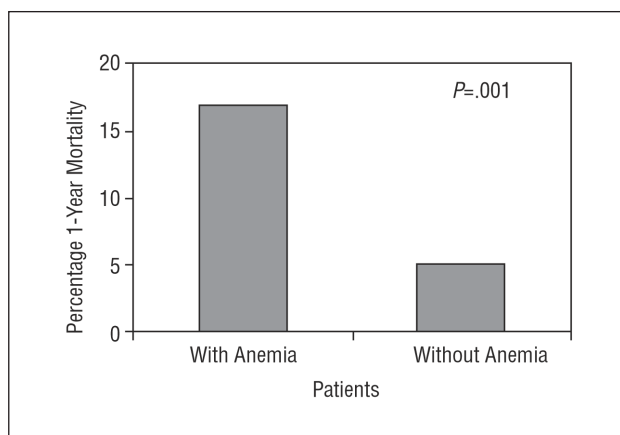
| Patients                 | n (%)    |
|--------------------------|----------|
| Survivors                | 309 (92) |
| Deaths                   | 28 (8)   |
| Without admission for HF | 271 (80) |
| With admission for HF    | 66 (20)  |
| 1 admissions             | 37 (11)  |
| 2 admissions             | 13 (4)   |
| 3 admissions             | 7 (2)    |
| >3 admissions            | 9 (3)    |

HF may play a role in this relationship but we do not have sufficient data to support this theory. Although Horwich et al<sup>5</sup> discuss the possible relationship between anemia and malnutrition, they do so on the basis of the relationship observed with albumin levels and body mass index, without reference to cholesterol<sup>5</sup>.

More and more attention is being paid to anemia in patients with HF due to the relationship between ane-



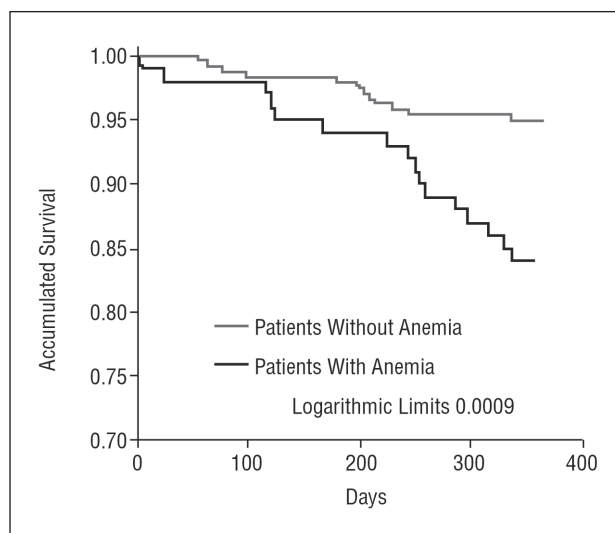
**Figure 2.** Graph showing means and standard deviations of hemoglobin levels for survivors and patients who died at 1 year of follow-up.



**Figure 3.** One-year mortality in patients with and without anemia on initial visit.

mia and HF prognosis which, in spite of all the new HF drug treatments available, continues to be poor.<sup>17</sup> Our data confirm that in Spain, anemia is clearly associated with a poor prognosis of HF. This association was reported by other authors<sup>4-9</sup> for mortality and HF-related need for readmission. Moreover, the same association was found in hospitalized patients<sup>4,7,9</sup> and out-patients.<sup>5,8</sup> Nonetheless, we found that plasma Hb levels maintained statistical significance in the multivariate analysis for mortality and HF-related admission. Anemia is reported to be an independent prognostic factor in patients with HF in more extensive series.<sup>5,7-9</sup> Mozaffarian et al<sup>8</sup> found a 1% reduction in hematocrit was associated with a 3% increase in risk of death in a series of 1130 patients with a mean follow-up of 15 months. Felker et al<sup>9</sup> found a 12% increase in the risk of suffering an event per 1 g/dL reduction in plasma Hb decrease in relation to a combined outcome of death and hospitalization at 60 days in a series of 949 patients<sup>9</sup>. Kosiborod et al<sup>7</sup> also found a 2% increase in 1-year mortality per 1% reduction in hematocrit and a 2% increase in risk of readmission at 1 year per 1% reduction in hematocrit. We found a 40% reduction in risk of death at 1 year per 1 g/dL increase in Hb and a 21% reduction in risk of HF-related admission at 1 year. This supports the argument in favor of correcting anemia when treating HF as the use of erythropoietin and iron has been shown to benefit patients<sup>2,18,19</sup>. On the other hand, in a small series, Androne et al<sup>6</sup> found that, in patients with HF, anemia due to hemodilution had a worse prognosis than true anemia, probably because of the greater volume overload and higher pulmonary capillary wedge pressure that hypervolemia generates.

Whether the association between anemia and a worse prognosis in patients with HF is chance or whether anemia is simply a risk marker remains unclear. The initially favorable results of these studies with erythro-



**Figure 4.** Kaplan-Meier survival curves for patients with and without anemia.

poinetin and iron, the prejudicial hemodynamic effects and the chance that anemia may favor myocardial ischemia support the possible cause-effect relationship. Treatment of anemia in patients with HF has improved prognosis for admissions<sup>2,18,19</sup> and significantly improved functional capacity<sup>20</sup>.

### Limitations of the Study

The study sample was drawn from the general population with HF attended in a specific, multidisciplinary HF unit of a tertiary hospital but this does not mean a complete absence of selection within the total population of patients with HF. The patients enrolled were mainly drawn from the Cardiology service, predominantly male, with ischemic etiology and relatively young. Therefore, the results can not necessarily be extrapolated to the overall population with HF. Hemoglobin level data we analyzed were obtained at a specific time (on first visit to the unit) and we did not evaluate changes occurring during the evolution of the illness or to patients' clinical situation. We do not have data on causes or treatment of anemia so these were not analyzed in the present study.

### CONCLUSIONS

Hemoglobin levels are important, independent prognostic indicators of mortality and HF-related admissions in patients with HF. The prevalence of anemia is seen to be important in a general population attended in a multidisciplinary HF unit. Hemoglobin levels correlate with a range of demographic, clinical, biochemical and therapeutic parameters, especially, age, gender, functional class and plasma levels of urea and cholesterol.



## ACKNOWLEDGEMENT

To Dr. J. López-Ayerbe for his collaboration and help in constructing the HF Unit database and in analyzing the results.

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