Table 3
In-hospital management according to the presence or absence of hyponatremia.

	Total $n=1659$	Hyponatremia $n=176$	No hyponatremia $n=1483$	p-Value
Diuretics, %				
Loop, i.v.	70.7	75.0	70.2	0.190
Loop, p.o.	88.8	86.9	89.0	0.409
Thiazide	5.4	9.1	4.9	0.020
Spironolactone	51.7	59.1	50.8	0.038
Inotropic agents, %				
Digoxin, i.v.	10.7	8.0	11.0	0.215
Digoxin, p.o.	33.8	35.8	33.6	0.561
Dopamine	20.3	34.7	18.6	<0.001
Dobutamine	12.7	26.1	11.1	<0.001
Norepinephrine	3.3	6.2	2.9	0.018
PDE III inhibitor	4.5	8.0	4.0	0.018
Vasodilator agents, %				
Nitroglycerin, i.v.	14.5	10.2	15.0	0.086
Isosorbide dinitrate, i.v.	12.1	13.6	11.9	0.498
Nitroglycerin, p.o.	3.1	2.3	3.2	0.513
Isosorbide dinitrate, p.o.	12.1	14.9	11.8	0.242
Carperitide	33.7	40.3	32.9	0.048
Procedures, %				
Mechanical ventilation	9.1	14.3	8.5	0.014
PCI	4.0	8.9	3.5	0.001
CABG	1.0	1.8	0.9	0.272
Pacemaker	4.4	7.2	4.0	0.058
Hemodialysis	3.1	7.8	2.6	<0.001
IABP	1.0	1.8	0.9	0.268
PCPS	0.2	0.6	0.1	0.191
LVAD	0.1	0.6	0.1	0.066

PDE, phosphodiesterase; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; DC, direct current cardioversion; IABP, intra-aortic balloon pumping; PCPS, percutaneous cardiopulmonary support; LVAD, left ventricular assist device.

In-hospital outcomes

Of the total cohort of patients, 37.7% were admitted from the emergency room; 34.8% of them stayed in the CCU, and mean length of CCU stay was 6.5 ± 10.2 days (median 4.0 days). Mean length of hospital stay was 33.8 ± 34.8 days and the median was 25.0 days. Crude in-hospital mortality was 5.7% (Table 4).

Patients with hyponatremia were more often admitted from emergency room (51.4% versus 36.1%, $p<0.001$) and stayed in the CCU (46.0% versus 33.4%, $p=0.001$). Moreover, their length of hospital stay was significantly longer (43.3 ± 37.0 days versus 32.8 ± 34.4 days, $p<0.001$).

Crude in-hospital mortality was significantly higher in patients with hyponatremia (13.3% versus 4.6%, $p<0.001$). In logistic regression model with patients without hyponatremia as the reference, hyponatremia was significantly associated with in-hospital death [unadjusted odds ratio (OR) 3.029, 95% confidence interval (CI) 1.819–5.043, $p<0.001$]. Even after adjustment for covariates, including medical history, NYHA functional class on admission, and medication use before hospitalization, hyponatremia was independently associated with in-hospital death (adjusted OR 2.453, 95% CI 1.265–4.755, $p=0.008$).

Long-term outcomes

During the follow-up after hospital discharge (mean 776.6 ± 294.9 days, 2.1 ± 0.8 years), the rates of adverse outcomes were as follows: all-cause death 22.2%, cardiac death 14.7%, and rehospitalization due to worsening HF 35.6%. Hyponatremia was significantly associated also with adverse long-term outcomes including all-cause death (OR 1.952, 95% CI 1.433–2.657, $p<0.001$), cardiac death (OR 2.053, 95% CI 1.413–2.983, $p<0.001$), rehospitalization due to worsening HF (OR 1.488, 95% CI 1.134–1.953, $p=0.004$), and all-cause death or rehospitalization due to worsening HF (OR 1.685, 95% CI 1.331–2.132, $p<0.001$) (Table 5 and Fig. 2). Even after adjustment with covariables including age, ischemic etiology, medical history, NYHA functional class on admission, medication use on admission, and laboratory data on admission, hyponatremia was an independent risk factor for all-cause death (adjusted OR 1.658, 95% CI 1.112–2.473, $p=0.013$), cardiac death (adjusted OR 1.775, 95% CI 1.075–2.929, $p=0.025$), and all-cause death or rehospitalization due to worsening HF (adjusted OR 1.526, 95% CI 1.114–2.042, $p=0.004$) (Table 5).

The results of subgroup analysis for all-cause death stratified by age (≥70 versus <70 years), sex, comorbidity (hypertension versus no hypertension and eGFR <60 mL/min/1.73 m^2 versus

Table 4
In-hospital outcomes according to the presence or absence of hyponatremia.

	Total $n=1659$	Hyponatremia $n=176$	No hyponatremia $n=1483$	p-Value
Visit to emergency room, %	37.7	51.4	36.1	<0.001
Stay at CCU, %	34.8	46.0	33.4	0.001
Length of CCU stay, days	6.5 ± 10.2	8.3 ± 14.9	6.2 ± 9.2	0.060
Length of hospital stay, days	33.8 ± 34.8	43.3 ± 37.0	32.8 ± 34.4	<0.001
In-hospital mortality, %	5.7	13.3	4.6	<0.001

CCU, coronary care unit. Data are shown as percent or means ± SD.

Table 5
Relative risk of long-term adverse outcomes associated with hyponatremia.

	OR (95% CI)	*p*-Value
All-cause death		
Unadjusted	1.952 (1.433–2.657)	<0.001
Adjusted	1.658 (1.112–2.473)	0.013
Cardiac death		
Unadjusted	2.053 (1.413–2.983)	<0.001
Adjusted	1.775 (1.075–2.929)	0.025
Rehospitalization due to heart failure		
Unadjusted	1.488 (1.134–1.953)	0.004
Adjusted	1.341 (0.955–1.884)	0.090
All-cause death or rehospitalization		
Unadjusted	1.685 (1.331–2.132)	<0.001
Adjusted	1.526 (1.114–2.042)	0.004

Relative risk was calculated after adjustment with covariables including age, ischemic etiology, medical history (hypertension, diabetes mellitus, sustained ventricular tachycardia/ventricular fibrillation, prior stroke), New York Heart Association functional class on admission, medication use on admission (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, βblocker, diuretics, aldosterone antagonist, warfarin), laboratory data on admission (estimated glomerular filtration rate, hemoglobin, plasma B-type natriuretic peptide). OR, odds ratio; CI, confidence interval.

≥60 mL/min/1.73 m^2), LVEF <40% versus ≥40%, and diuretic use versus no diuretic use are shown in Table 6. There was no significant interaction in any subgroups. These results showing that hyponatremia was associated with all-cause death in each subgroup were similar to those found on the primary analysis.

Discussion

The present study demonstrated by using the JCARE-CARD database that, among patients hospitalized with worsening HF, hyponatremia was seen in 10.6% of patients. Patients with hyponatremia had more comorbidities. Plasma BNP was significantly higher, and eGFR and hemoglobin concentration were lower in these patients. Importantly, the risks of adjusted in-hospital mortality as well as long-term adverse outcomes including all-cause death, cardiac death, and rehospitalization due to HF were significantly higher in patients with hyponatremia.

The present study demonstrated that hyponatremia was associated with not only adverse in-hospital but also long-term outcomes in patients hospitalized with worsening HF. The present results were consistent with previous reports [1–4]. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study identified a substantial risk of short- and intermediate-term clinical events associated with decreasing serum sodium concentration in patients hospitalized for worsening HF [1]. Lower serum sodium concentrations on admission remained a predictor of increased number of days hospitalized for cardiovascular causes and increased mortality within 60 days of discharge even after adjustment for a variety of baseline variables [1]. In the OPTIMIZE-HF registry, low serum sodium was more common among patients with lower admission systolic blood pressure and a prior history of HF [2]. After adjusting for differences with multivariable analysis, the risk of in-hospital death increased by 19.5%, for each 3 mmol/L decrease in patients with serum sodium <140 mmol/L [2]. The Italian Registry on Heart Failure Outcome (IN-HF) also demonstrated that hyponatremia (serum sodium concentration <136 mEq/L) was one of the independent predictors of in-hospital mortality (OR 2.00, 95% CI 1.26–3.19, $p = 0.004$) [16]. However, these studies have primarily focused on in-hospital and early post-discharge mortality. Moreover, the OPTIME-CHF study, was performed using the patient data derived from a large clinical trial with restricted inclusion criteria, such as markedly reduced LVEF of ≤30%, lower serum creatinine levels of ≤3 mg/dL, and systolic blood pressure ≥80 mmHg [1]. The present study extended the prognostic impact of hyponatremia during the long-term follow-up over 2 years and more importantly to a non-selected HF population encountered in routine clinical practice by analyzing the registry data of hospitalized HF patients in Japan.

There are several mechanisms of hyponatremia responsible for worsening clinical outcomes in HF. First, hyponatremia may directly reflect the reduction of cardiac output. Reduced cardiac output decreases renal perfusion and GFR. Previous studies [17–19] including our own [6] demonstrated that reduced GFR was

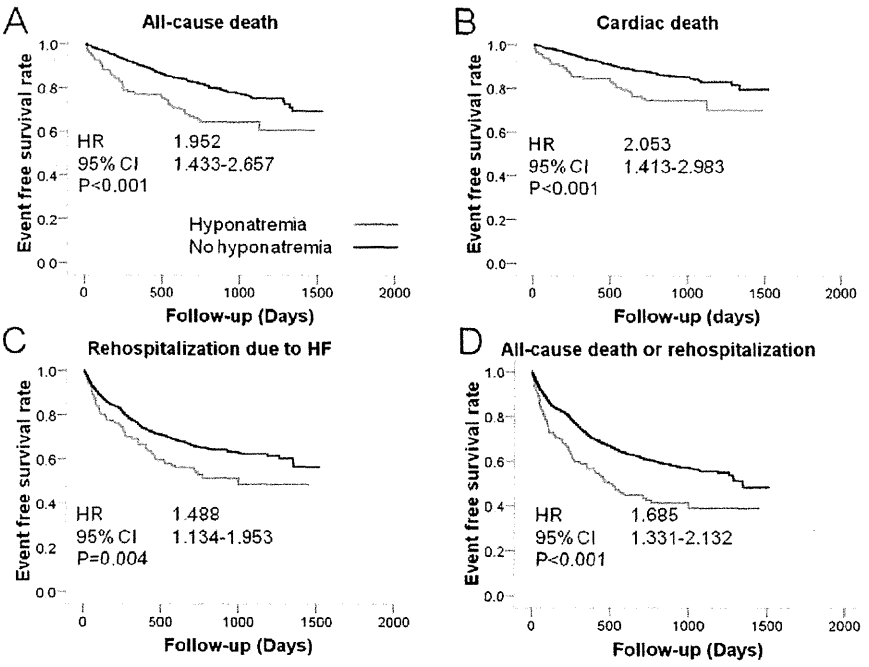

Fig. 2. Kaplan–Meier survival curves free from all-cause death (A), cardiac death (B), rehospitalization due to worsening heart failure (HF) (C), and all-cause death or rehospitalization (D) according to the presence or absence of hyponatremia.

Table 6
Subgroup analysis for relative risk of all-cause death associated with hyponatremia.

Subgroup	*n*	OR for all-cause death	95% CI	*p*-Value	
		Na <135 mEq/L vs. ≥135 mEq/L		Between groups	Interaction
Age <70 years old	558	2.257	1.300–3.920	0.004	0.767
Age ≥70 years old	805	2.042	1.405–2.968	<0.001	
Male	807	2.046	1.396–2.998	<0.001	0.699
Female	556	1.827	1.080–3.092	0.025	
Hypertension	708	1.945	1.184–3.197	0.009	0.981
No hypertension	646	1.920	1.293–2.852	0.001	
eGFR <60 mL/min/1.73 m^2	867	1.940	1.395–2.696	<0.001	0.442
eGFR ≥60 mL/min/1.73 m^2	494	1.362	0.544–3.413	0.510	
LVEF <40%	592	1.544	0.927–2.573	0.095	0.373
LVEF ≥40%	629	2.125	1.333–3.386	0.002	
Diuretic use	838	2.021	1.442–2.832	<0.001	0.355
No diuretic use	525	1.344	0.615–2.938	0.459	

eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; OR, odds ratio; CI, confidence interval.

associated with worsening outcomes in patients with HF. Second, hormonal abnormalities are also important factors of hyponatremia in HF. Renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS) are activated in HF [20,21]. Increased SNS and RAAS cause renal vasoconstriction and reduce GFR. These hormonal abnormalities also increase the retention of sodium and water, and induce the release of arginine vasopressin (AVP). AVP increases vascular resistance and also increase free water retention [22–24]. It also directly and adversely affects myocardial contractility and cell growth [25]. Finally, hyponatremia may also result from the use of diuretics. Diuretic use has been consistently reported to be associated with long-term adverse outcomes in previous studies [26,27] including our own [28]. Therefore, it is not clear whether hyponatremia is directly associated with adverse outcomes in HF or only a marker of more advanced status of HF which requires the use of diuretics.

Given the prognostic role of hyponatremia in HF, the treatment of hyponatremia may improve outcomes in patients with HF. Tolvaptan is a V2 receptor antagonist approved for the treatment of hyponatremia (serum sodium <125 mEq/L) in patients with cirrhosis, HF, and syndrome of inappropriate anti-diuretic hormone secretion in the USA and also fluid retention in HF patients in Japan. Tolvaptan significantly increased serum sodium concentration in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST). However, it had no beneficial effects on long-term mortality or HF-related morbidity [29]. Furthermore, in the subanalysis of the EVEREST study for HF patients with hyponatremia (11.5% of total cohort), tolvaptan use was associated with greater likelihood of normalization of serum sodium, greater weight reduction at day 1 and discharge, and greater relief of dyspnea than placebo. However, long-term outcomes were comparable between patients with tolvaptan and placebo. Only in 92 patients with pronounced hyponatremia (<130 mEq/mL), tolvaptan was associated with reduced cardiovascular morbidity and mortality after discharge ($p = 0.04$) [30]. Further clinical studies are clearly needed to determine the effects of tolvaptan on the outcomes of hyponatremic HF patients. Moreover, tolvaptan is not necessarily a therapeutic tool for hyponatremia, and is one of diuretics. Thus, it may not be easy to clarify the effects of a therapeutic intervention against hyponatremia by analyzing the effects of tolvaptan.

Study limitations

Several limitations inherent in the design of the registry should be considered in this study. First, the documentation of serum sodium concentration levels on admission might not accurately reflect those after discharge or their changes over time. Second, the present study was not a prospective randomized trial and, despite covariate adjustment, other measured and unmeasured factors might have influenced outcomes. Third, we did not collect information regarding the dose of loop diuretics and cannot assess its relation to prognosis. Loop diuretic use can induce hyponatremia and has been demonstrated to be associated with worse outcomes in our previous study [28]. Finally, data were dependent on the accuracy of documentation and abstraction by individual cardiologists that participated in this study.

Conclusions

Hyponatremia was observed in 10% of patients hospitalized with worsening HF. It was independently associated with in-hospital as well as long-term adverse outcomes in these patients. Further studies are needed to establish serum sodium concentration as a potential therapeutic target for HF.

Acknowledgments

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循環器内科学

心不全の予後を予測することはできるのか？

——心不全数式化への挑戦

Is it possible to predict the prognosis of patients with heart failure?
——A challenge to establish a mathematical formula for characterizing heart failure

心不全とは，何らかの構造的あるいは機能的な心臓の異常で心臓のポンプ機能が低下することによって，有効な血液循環が保たれなくなる状態を示す複合的な症候群である[1]．したがって，心不全を引き起こす背景因子や原因は多種多様であり，心不全に至る病態生理も一様ではない．つまり心筋梗塞や狭心症，心臓弁膜症，心筋症などの循環器疾患はもとより，高血圧や糖尿病などの有病率の高い生活習慣病も心不全の原因となることから，それらの終末像である心不全に至る病態を適切かつ効率的に把握し管理することは循環器専門医の重要な命題であるが，心不全が悪性新生物と並び日本の死因の最上位であることから，医療界全体にとっても重要な課題であるといえる．心不全の予後をいまよりも正確に予測することができれば，適切な時期に適切な処置(投薬やデバイスの導入など)を行うことが可能となり，健康寿命の延長や医療経済上の効果に資するものと考えられる．

テーラーメード医療の実現に向けて

心不全の予後，つまり心不全を原因とする死亡や入院に関与するリスクを推定して層別化し介入することは可能なのであろうか．心不全の予後に寄与する因子を推定する数多くの研究がいままで行われ，それらの結果をもとにしたメタ解析によると，いくつかの因子が絞り込まれてきている[2,3]．しかし，これらの因子を用いた予後予測を実臨床に演繹しようとする場合に，背景因子や病態が異なる個々の患者においてかならずしも当てはまるわけではなく，こうした手法の限界がみえてくる．個別医療においては個々の患者の個体間格差が大きく，的確な診断，適切な治療，正確な予後予測を行うに医師のそれまでの経験や裁量，あるいは臨床研究からのエビデンスに頼るところが大きく，画一した方法がないことが問題である．一方，集団医療において明らかにされてきたエビデンスは数理的・平均的であり，診断基準や治療ガイドラインの策定にはおおいに貢献してきた．個別医療と集団医療の利点を十分に活かして有効に活用するためには真に臨床に演繹できるエビデンスが必須であり，これにより個別医療と集団医療をリンクさせた患者個々の病態に即したテーラーメード医療が提供できるものと著者らは考えている(図1)．この考えに基づいて著者らは，個々の患者の状態に即した心不全予後を推定する数式の作成に関する研究を行っている．

心不全の予後を数式で算出することはできるのか？

静止位置からの自由落下運動において，物体の位置(z)は落下開始からの時間(t)と重力加速度(g)とで表され($z=gt^2/2$)，物体の重さや大きさには依存しない．自然科学の一分野である生物学や基礎医学は数理的構造をその学問のなかに内在しているため，その領域において数学的な解を得ることや再現性のある事象を観察することが可能である．この物理学の考えを生物学，医学にも当てはめ，心不全を含めた疾患の進行(Z)も罹患からの時間(T)と疾患構造(G)によって説明できるのではないかと著者らは考えた．しかし，現実世界では物体の大きさや形によってさまざまな空気抵抗を受け，風力などの外的要因によっても物体の位置(z)は影響を受ける．これと同様に，疾患の進行(Z)も多種多様な要因によって影響を受けることは自明であり，また疾患構造(G)も経時的に変化するかもしれ

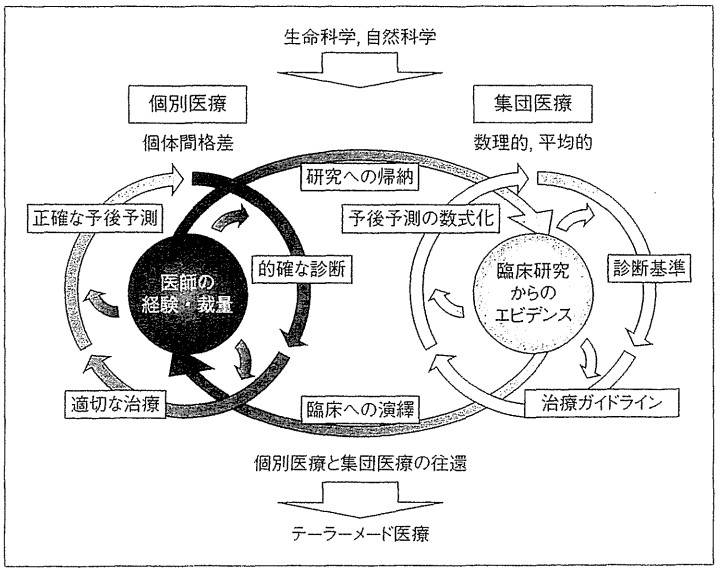

図 1　個別医療と集団医療

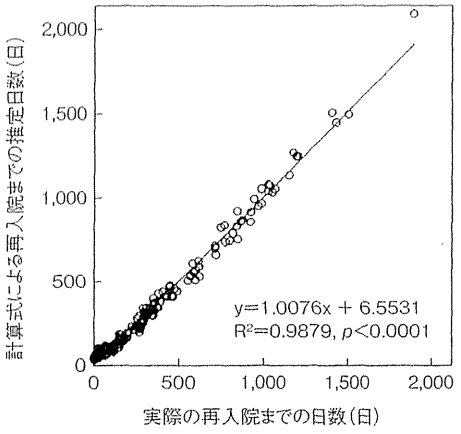

図 2　数式から求めた死亡または心不全による再入院までの推定日数と実測日数[4]

ない．そこで著者らは，心機能のみならず，腎機能，肝機能，消化管機能，不眠，便秘，在宅介護者の有無など他臓器，精神神経状態，社会的要因を加味したさまざまな要因(Xi)と退院後の死亡または心不全による再入院までの日数(Yi)を予測する関数式($Yi=\max(T)/\beta T\cdot\{Xi/\max(X)\}+c$)を後向き研究で導き出した．さらに，この関数式から求めた死亡または心不全による再入院までの推定日数は実測日数と非常に近く(図2)，良好な相関を示すことも確認した[4]．現在は本研究成果の妥当性を検証するために前向き観察研究を実施しているところである．

より高精度の心不全予後予測式を作成するために

心不全の予後に関与すると考えられる因子は非常に多岐にわたり，それらのすべてを同定したうえで包含した解析を行うことは事実上不可能である．現在に至るまで心不全予後を予測する多くの研究が行われてきたが，研究ごとに解析対象とする因子は異なり，いままでの臨床経験やそれまでの論文による報告，研究者の直観などによって解析対象とする因子は選択されてきた．そのなかからもっとも関与が高いと考えられる因子を多変量解析で抽出して予後規定因子として報告されている．選択する因子の組合せによっても結果は変化することから，どのような因子の組合せがもっとも適切かという問いに対する答えを出すことは非常に困難である．そこで著者らは，診療録における患者情報，各種検査結果，投薬内容などの膨大な臨床データを集約できるシステムの開発を行い，数学の専門家との共同研究で網羅的に心不全予後に関与する因子の同定を行い，精度の高い心不全予後推定式の作成に取り組んでいるところである．

おわりに

心不全の予後を予測することができるかどうかについては，著者らが算出した式の妥当性を検証する前向き研究の結果をもって判断する必要があると考えている．この研究は数学的構造を生物学や医学のなかに仮定することへの妥当性を心不全という病態を用いて検証しようとする試みであり，いままでにないまったく新しい発想に基づいた挑戦的な研究であると考えている．

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「心不全」再発を予測

阪大開発 薬歴・血液などで時期算出

急性心不全を発症した患者の症状再発時期を予測する計算方法を開発したと、大阪大産業科学研究所の鷲尾隆教授(知能情報学)らの研究グループが発表した。血液データや家族構成、便秘薬の使用の有無など252項目を入力し、算出する。がん再発予測の計算モデルはあるが、循環器系の疾患では初めてだという。

研究には、国立循環器病研究センター(国循、大阪府吹田市)が協力した。2006年5月～09年12月、国循に急性心不全で入院した486人について、薬歴や血液などの検査結果、性別、家族構成などのデータ750項目を調べた。その結果、252項目が再発と関係している可能性があることが分かった。

再発までの期間は配偶者がいる人の方がいない人より平均134日長かった。睡眠薬を使わない人の方が使う人より229日、便秘薬を使わない人の方が使う人より718日、再発までの期間が長い傾向があった。解析結果と患者の実際の再発までの日数との誤差は最大約1カ月だった。今後、他病院の患者データなどを使い、有効性を検証する。

鷲尾教授は「モデルを使えば、再発を防ぐためにより適切な治療や生活指導ができる」と話している。【吉田卓矢】

心不全 再発確率の推定法開発

男性は女性の1.85倍
独身は既婚の1.24倍

阪大・国立循環器病研究センター

大阪大と国立循環器病研究センター（大阪府吹田市）は、一度心不全になった患者が急性心不全を再発する確率や再入院する時期を精度良く推定する方法を開発した。血圧や薬の種類など252項目のデータを使えば、入院時期を誤差1カ月程度で推定できるという。再発確率を下げる治療方針作りに役立ちそうだ。

国循は2006～09年に心不全で入退院した486人について、入院記録や性別、使った薬、家族構成など750項目のデータを提供。阪大産業科学研究所の鷲尾隆教授（知能情報学）らが、どのデータが退院後の再発や再入院と関係が深いかをコンピューターで網羅的に分析した。

その結果、因果関係は不明だが、750項目のうち252項目が重要だとわかった。最高・最低血圧が高いことや便秘、睡眠薬の利用は再発確率を高め、配偶者がいることや女性であることは低くする方向に働くという。

国循の北風政史・臨床研究部長は「社会的な要因も関係していることは驚きだった」と話す。

今は北海道大や九州大なども研究に加わり、推定法が実際の治療に役立つかどうか確かめている。鷲尾さんは「他の病気にも応用できるかもしれない」という。

（小堀龍之）

■心不全の再発確率を上げる要因の例

	再発確率(※)
男性である	女性の1.85倍
便秘薬を飲んでいる	飲んでいない人の2.7倍
睡眠薬を飲んでいる	飲んでいない人の1.44倍
結婚していない	結婚している人の1.24倍

※再発までの平均日数から算出。因果関係は不明。