Chronic dialysis patient with severe secondary hyperparathyroidism undergoing parathyroidectomy in Indonesia: a case series

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ABSTRACT

Background: Parathyroidectomy is a method of treating secondary hyperparathyroidism associated with Chronic Kidney Disease (CKD), which has been largely abandoned in developed countries due to the existence of calcimimetic drugs which are reported to be effective in treating secondary hyperparathyroidism in this population. However, in developing countries like Indonesia, the availability of Calcimimetic drugs is still rare and expensive, so that parathyroidectomy can be an option. The study aimed to present four case reports of chronic HD patients with SHPT accompanied by clinical symptoms. As far as our knowledge goes, this is the first case series reported from Indonesia.

Case Presentation: This research is a multicenter case series study. All patients had undergone dialysis for five years and complained of body aches. All calcium levels were within the normal range, while three patients had hyperphosphatemia and one patient had normal phosphate levels. All patients had iPTH levels > 1000 pg/ml in the last six months. Before the surgery, all patients had received long-term phosphate-binding drugs, including calcium-based and non-calcium-based drugs and vitamin D3 agonists. All patients underwent total parathyroidectomy with autotransplantation of parathyroid tissue in the right antebrachial regions, except for the second patient who received the transplant in the left antebrachial region due to an AV fistula in the right arm.

Conclusion: In dialysis patients, especially in developing countries, approximately 10.7% of them experience SHPT with PTH levels > 1,000 pg/mL, and one study in Indonesia showed that around 35% of patients undergoing chronic hemodialysis had PTH levels > 200 pg/mL, making parathyroidectomy a highly possible option considering that medications such as cinacalcet are more expensive and not widely available.

Keywords: Dialysis, Hyperparathyroidism, Parathyroidectomy, Case Series.


INTRODUCTION

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD), which occurs in >50% of stage 3 and 4 CKD patients and 90% of patients with end-stage kidney disease (ESKD). Impaired phosphate excretion and decreased synthesis of active vitamin D lead to increased serum phosphate and decreased serum calcium, which directly stimulate parathyroid hormone (PTH) secretion. Interestingly, there is persistent elevation of PTH, calcium, and phosphate, with clinical manifestations ranging from asymptomatic to functional impairment related to bone fractures due to decreased bone density. Symptoms such as severe pruritus, body pain, cognitive impairment, and calciphylaxis are also frequently encountered and impair the quality of life of dialysis patients. The incidence of cardiovascular events, anemia hyporesponsive to erythropoietin (EPO), and all-cause mortality in CKD patients with SHPT is also significantly increased.

The management of SHPT is quite challenging. A drug called calcimimetics/cinacalcet (oral) and etelcalcetide (iv), approved in 2004 and 2017, has been shown to improve PTH, calcium, and phosphate levels and is generally used in chronic hemodialysis (HD) patients. In a recent study, cinacalcet significantly reduced the need for parathyroidectomy. However, this drug has side effects related to vomiting and diarrhea and is not widely available in many countries. Due to these side effects combined with socioeconomic constraints, non-compliance related to cinacalcet is reported to be very high. In addition, many patients do not respond adequately and eventually are referred to a surgeon for consideration of parathyroidectomy. Parathyroidectomy is a safe and effective therapy for treating SHPT in dialysis patients, and many patients meet the indications. Still, it turns out that about 81% of patients do not receive it, perhaps because there is no universal guideline determining the appropriate time for parathyroidectomy and concerns about long-term postoperative complications.

The study aimed to present four case reports of chronic HD patients with SHPT accompanied by clinical symptoms. As far as we know, this is the first case series reported from Indonesia. These patients experienced clinical and biochemical improvement after undergoing parathyroidectomy.
CASE REPORT

This research is a multicenter case series study. This case series has been reported in line with the PROCESS Guideline. The patients in this case series varied in age and comorbidities and included both male and female patients. They had undergone dialysis for five years or more and complained of body aches. All calcium levels were within the normal range, while three patients had hyperphosphatemia and one patient had normal phosphate levels. All patients had iPTH levels >1000 pg/ml in the last six months. Before the surgery, all patients had received long-term phosphate-binding drugs, including calcium-based and non-calcium-based drugs and vitamin D3 agonists. Ultrasound examination of the parathyroid glands prior to surgery showed enlargement of the parathyroid glands. All patients underwent total parathyroidectomy with autotransplantation of parathyroid tissue in the right antebrachial regions, except for the second patient who received the transplant in the left antebrachial region due to an AV fistula in the right arm. The same surgeon performed the surgeries. Unfortunately, there is no data available on radiological examination of the bone (Table 1).

During hospitalization, calcium and phosphorus levels were checked every 6-12 hours until they stabilized, and more often as needed based on the patient's conditions. All patients experienced symptomatic hypocalcemia postoperative, including hand/foot and perioral numbness and muscle cramps. They received iv calcium gluconate therapy immediately after surgery with varying doses depending on their calcium levels and condition, which were titrated accordingly. The third patient had severe and prolonged hypocalcemia consistent with hungry bone syndrome (HBS). The maximal doses of iv calcium gluconate to each patient were 540 mg/24 hours (first and second patient), 1.35 grams/24 hours (third patient), and 270 mg/24 hours (fourth patient). From day 2-4 after surgery, all patients were given companion oral drugs such as calcium carbonate, vitamin D3 agonists, and bisphosphonates. All patients’ serum phosphorus levels returned to the normal range after surgery (Figure 1).

All patients experienced a gradual relief of pain and itching symptoms 1-2 weeks postoperative. The length of hospital stay varied from 4 to 7 days.

Cases Presentation

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Table 1. Summary Data of Patients Undergoing Parathyroidectomy

<table>
<thead>
<tr>
<th>Variables</th>
<th>First Patient</th>
<th>Second Patient</th>
<th>Third Patient</th>
<th>Fourth Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40 years old</td>
<td>67 years old</td>
<td>28 years old</td>
<td>39 years old</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Diabetes 12 years, Hypertension 6 years</td>
<td>Hypertension 28 years</td>
<td>Hypertension 8 years</td>
<td>Hypertension 9 years</td>
</tr>
<tr>
<td>Duration of dialysis</td>
<td>5 years of hemodialysis (HD)</td>
<td>HD 7 years</td>
<td>Peritoneal dialysis (PD) 4 yrs, continue HD 1 year</td>
<td>HD 7 years</td>
</tr>
<tr>
<td>Preoperative complaints related to SHPT</td>
<td>Leg and back pain</td>
<td>Pain throughout the body</td>
<td>Pain throughout the body, Penguin-like gait, anxiety</td>
<td>Pain in the thigh area, pain when walking, itching</td>
</tr>
<tr>
<td>Routine oral medication</td>
<td>Nifedipine SR 1x30 mg, CaCO3 2x500 mg, Alfacalcidol 1x0.5 mcg</td>
<td>Irbesartan 1x150 mg, Sevelamer 1x800 mg, Alfacalcidol 1x0.5 mcg</td>
<td>Irbesartan 1x150 mg, Bisoprolol 1x2.5 mg, CaCO3 3x500 mg, Alfacalcidol 1x0.5 mcg</td>
<td>Carvedilol 1x12.5 mg, Alfacalcidol 1x0.5 mcg, calcium lactate 3x500 mg</td>
</tr>
<tr>
<td>Preoperative calcium level (last 3 months)</td>
<td>9.3-9.8 mg/dl</td>
<td>8.5-9.1 mg/dl</td>
<td>9.2-9.6 mg/dl</td>
<td>9.5-9.8 mg/dl</td>
</tr>
<tr>
<td>Preoperative phosphorus level (last 3 months)</td>
<td>7.5-8.5 mg/dl</td>
<td>2.5-2.9 mg/dl</td>
<td>5.1-5.7 mg/dl</td>
<td>6.8-7.2 mg/dl</td>
</tr>
<tr>
<td>Preoperative iPTH level</td>
<td>1035 pg/ml</td>
<td>1286 pg/ml</td>
<td>1370 pg/ml</td>
<td>2050 pg/ml</td>
</tr>
<tr>
<td>Preoperative ALP level</td>
<td>194 U/mL</td>
<td>467U/mL</td>
<td>156 U/mL</td>
<td>879 U/mL</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Total parathyroidectomy + autotransplantation</td>
<td>Total parathyroidectomy + autotransplantation</td>
<td>Total parathyroidectomy + autotransplantation</td>
<td>Total parathyroidectomy + autotransplantation</td>
</tr>
</tbody>
</table>

Figure 1. Postoperative Intravenous Serum Calcium and Phosphorus Levels During Hospitalization.
Table 2. Monitoring Post Operative Patients Undergoing Parathyroidectomy

<table>
<thead>
<tr>
<th>Variables</th>
<th>First Patient</th>
<th>Second Patient</th>
<th>Third Patient</th>
<th>Fourth Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical improvement</td>
<td>Pain disappeared</td>
<td>Pain disappeared</td>
<td>Pain disappeared</td>
<td>Pain and itch disappeared</td>
</tr>
<tr>
<td>Improvement in anemia</td>
<td>Hb 10-12 g/dL (without transfusion and EPO)</td>
<td>No difference (Hb 7.8-9.5 g/dl), EPO 2x/week</td>
<td>Hb 10-11 g/dl (without transfusion, EPO as needed)</td>
<td>Hb 9-11 g/dl (without transfusion, EPO as needed)</td>
</tr>
<tr>
<td>Improvement in blood pressure</td>
<td>Preop systolic BP 180-200 mmHg</td>
<td>Reduce half the dose of the anti-hypertension drug</td>
<td>Preop systolic BP 170-190 mmHg</td>
<td>Preop systolic BP 170-190 mmHg</td>
</tr>
<tr>
<td>Postop systolic BP 130-150 mmHg</td>
<td></td>
<td></td>
<td>Postop systolic BP 130-150 mmHg</td>
<td>Postop systolic BP 130-150 mmHg</td>
</tr>
<tr>
<td>Length of stay</td>
<td>7 days</td>
<td>10 days</td>
<td>15 days</td>
<td>7 days</td>
</tr>
<tr>
<td>Medications are given</td>
<td>Nifedipine SR 1x30 mg, Alfalcacidol 1x0.5 mcg, CaCO3 3x500 mg, 35 mg/week of biphosphonate.</td>
<td>Irbesartan 1x150 mg, Alfalcacidol 3x0.5 mcg, CaCO3 3x500 mg, biphosphonate 2x35 mg/week.</td>
<td>Irbesartan 1x150 mg, CaCO3 3x500 mg, Alfalcacidol 2x0.5 mcg, dan biphosphonate 35 mg/week.</td>
<td>Carvedilol 1x12.5 mg, CaCO3 3x500 mg, Alfalcacidol 3x0.5 mcg, biphosphonate 35 mg/week.</td>
</tr>
<tr>
<td>Adjustment of medications after follow-up</td>
<td>Nifedipine 1x30 mg, CaCO3 1x500 mg, 180 mg of calcium gluconate injection after HD</td>
<td>Irbesartan 1x75 mg, Calcium+D3 1x1, CaCO3 3x500 mg, biphosphonate 35 mg/week.</td>
<td>Irbesartan 1x150 mg, Calcium+D3 1x1, and CaCO3 3x500 mg.</td>
<td>Carvedilol 1x12.5 mg, Lactate Calcium 2x1, and Alfalcacidol 1x0.5 mcg.</td>
</tr>
<tr>
<td>Time elapsed since surgery until now</td>
<td>9 months (no recurrence of symptoms yet)</td>
<td>9 months (no recurrence of symptoms yet)</td>
<td>13 months (no recurrence of symptoms yet)</td>
<td>21 months (no recurrence of symptoms yet)</td>
</tr>
</tbody>
</table>

Figure 2. Serum iPTH Level Trends During Postoperativanavenous Follow Up.

ranged from 7-15 days, depending on the severity of hypocalcemic complications. Hemodialysis was carried out according to the schedule, with adjustments for specific conditions. At the follow-up, 9 months postoperative (first and second patients), 13 months postoperative (third patient), and 21 months postoperative (fourth patient), none of the patients experienced a recurrence of symptoms, persistent/relapsed SHPT, recurrent hypocalcemia, or death. Postoperative calcium and phosphorus levels were checked routinely every 1-3 months, and normal calcium ranges were found in all patients. Phosphorus levels tended to increase in all patients.

In contrast, iPTH levels fell >80% 1 day postoperative and gradually increased during follow-up but remained within the recommended range of 2-9 times the upper limit of normal (Figure 2). Normal calcium levels ranged from 8.4-10.2 mg/dl, and normal phosphorus levels ranged from 2.3-4.7 mg/dl. During follow-up, all patients continued taking calcium supplements and vitamin D3 agonists (Figure 3). Additionally, the second patient experienced a decrease in average blood pressure, and the dose of antihypertensive drugs was reduced by half. Three out of four patients also experienced an improvement in Hb levels and a decreased need for erythropoietin and blood transfusions. Pathological anatomy examination showed that all patients had parathyroid adenoma.

DISCUSSION

To improve the quality of care for dialysis patients with SHPT, consistent control of biochemical markers is highly predictive of survival. However, traditional treatment of SHPT with phosphate restriction, phosphate binding agents, calcium supplementation, and vitamin D often falls short of achieving targets. Other new therapies include calcitriol, alfalcacidol, active vitamin D analogs, cinacalcet hydrochloride, and non-calcium/aluminum-based phosphate binders to achieve consistent biochemical marker control, which may lead to hypercalcemia and/or hyperphosphatemia, associated with cardiovascular and soft tissue calcification, particularly with calcium salts and vitamin D. This requires cessation of treatment and potentially inadequate PTH control and disease progression. Calcimimetics
CASE REPORT

Figure 3. Long Term Follow Up of Calcium and Phosphorus Level After Surgery.

(cinacalcet) works by increasing the sensitivity of calcium-sensing receptors on parathyroid cells to extracellular calcium, thereby suppressing serum levels of PTH, calcium, and phosphorus, and have been reported to reduce the risk of bone fractures, cardiovascular disease, and parathyroidectomy.14

In dialysis patients, especially in developing countries, approximately 10.7% of them experience SHPT with PTH levels >1,000 pg/mL, and one study in Indonesia showed that around 35% of patients undergoing chronic hemodialysis had PTH levels >200 pg/mL, making parathyroidectomy a highly possible option considering that medications such as cinacalcet are more expensive and not widely available.16-17 Referral to a surgeon for parathyroidectomy is considered when maximal medical management has been carried out for at least 6 months in patients with refractory SHPT, such as with cinacalcet therapy, and modifiable factors such as hypocalcemia, vitamin D deficiency, and hyperphosphatemia have been addressed. At this point, the patient is considered to have refractory hyperparathyroidism.18 There is no universal definition for "refractory hyperparathyroidism". KDIGO suggests that the target range for PTH levels should be 2-9 times the normal upper limit (130-585 pg/mL if the upper limit of normal is 65 pg/mL). Some clinicians use a PTH level cutoff of >800 pg/mL (severe SHPT based on KDIGO) with hypercalcemia and/or hyperphosphatemia as a referral threshold for parathyroidectomy. Therefore, if persistent PTH levels are >585-800 pg/mL with hypercalcemia and/or hyperphosphatemia or considering a lower threshold in patients with symptoms/complications caused by SHPT, referral for parathyroidectomy may be indicated.16,18,19

There are 3 types of parathyroidectomy: subtotal parathyroidectomy, total parathyroidectomy, and total parathyroidectomy with autotransplantation of parathyroid tissue. Although total parathyroidectomy is often performed to prevent a recurrence, it is not favored due to the risk of permanent hypocalcemia and HBS. In addition, excessively low PTH levels also have detrimental effects.19 The advantage of total parathyroidectomy with autotransplantation is that it is easy to perform parathyroidectomy if recurrence occurs as it can be accessed with local anesthesia.4 This technique can cause recurrent SHPT but less than subtotal parathyroidectomy.20,25 One meta-analysis in 2019, more than 3600 dialysis patients with SHPT, did not show a statistically significant difference between total parathyroidectomy with autotransplantation and subtotal parathyroidectomy in terms of incidence of hypocalcemia, radiological improvement in bone disease, improvement in symptoms related to SHPT, persistent rate, and disease recurrence.22 The autotransplanted parathyroid tissue will not function until neovascularization occurs. Autograft parathyroid tissue tends to be stable in most patients, at least up to 36 months after surgery. This tissue is sensitive to calcium and the uremic environment, so its response is physiological as long as the implanted tissue is still autonomous.23 At the 9-21 months follow-up after surgery, all patients still required calcium supplements and/or vitamin D analogs, same as one of the study results that total parathyroidectomy with autotransplantation group tended to require long-term calcium and vitamin D supplementation.22

One of the most common postoperative complications of parathyroidectomy is hypocalcemia, which can be caused by postoperative hypoparathyroidism or HBS and must be differentiated. HBS is defined as a decrease in serum phosphorus and calcium levels to <8.4 mg/dl, typically peaking on day 2-4 postoperative and/or prolonged hypocalcemia after day 4 postoperative, resulting from rapid bone remineralization due to removal of high bone turnover stimulation (such as high PTH).24 HBS often requires iv calcium replacement for an average of 7 days postoperative, followed by high-dose calcium and vitamin D analog supplementation. Serum calcium levels decrease for at least 3 weeks after surgery, lasting several days to several months, and rarely for >1 year.26-28 Third patient likely experienced HBS (1 out of 4 patients ~ 25%), the same prevalence as reported before was approximately 25-27.4%.25,26 Due to previous studies, HBS's risk factors include radiological evidence of osteitis fibrosa cystica, younger age <45 years, higher pre-op ALP (>120 IU/L), a larger volume of parathyroid gland resected, and lower preoperative serum calcium levels.25,26,28-31

Cozzolino et al. 2004 proposed an intravenous calcium gluconate dose with a rate of 1-2 mg/kg/hour, which can be increased or decreased by 25-50% from the initial value.32 Loke et al. in 2009 developed a titration algorithm in which a 10% calcium gluconate infusion is started at 4.5 mL/hour when serum calcium levels are <8 mg/dL and then increased to 6.5 mL/hour and eventually to 9.5 mL/hour if calcium levels continue to decrease.33 Chou et al. proposed that all patients receive 2 grams of intravenous calcium gluconate infusion immediately after surgery, followed by a serum calcium level check 18 hours...
after surgery, which will determine the subsequent dose of iv calcium gluconate to be given.\textsuperscript{31} The goal is to increase the ionized serum calcium concentration to the normal range, maintain it, and control the patient's symptoms. As soon as possible, oral calcium supplementation should be started with a recommended dose of 1-2 g of calcium carbonate three times daily (a total of 1.2-2.4 g/day of elemental calcium) and, if necessary, supplemented with vitamin D or its analogs with range dose 0.5-4 mcg/day according to calcium levels.\textsuperscript{24,31,34} High-calcium dialysate may also be considered in dialysis patients to help manage postoperative hypocalcemia.\textsuperscript{34}

The analog vitamin D drugs commonly used are calcitriol, paricalcitol, and alfalfacacido. Calcitriol increases intestinal calcium absorption and enhances bone metabolism by inhibiting osteoclasts and promoting osteoblasts. Oral and iv administration can be used to treat SHPT.\textsuperscript{35} Calcitriol is more effective than alfalfacacido in reducing serum PTH, but it often induces hypercalcemia and hyperphosphatemia.\textsuperscript{36} Paricalcitol is a selective vitamin D receptor activator that significantly reduces PTH secretion without affecting calcium and phosphorus levels and has a good safety profile. The incidence of hypercalcemia and hyperphosphatemia is lower compared to calcitriol.\textsuperscript{37,38} Our patients used alfalfacacido as their activator of vitamin D3 analog. During the 9-21 months of follow-up after surgery, none of the patients experienced hypercalcemia, but their serum phosphorus levels continued to increase, possibly due to their diet. Since the surgery, phosphate binders were still given, with the option of using calcium-based phosphate binders.\textsuperscript{39}

There is no universal definition of "cure" for SHPT. The benefits of parathyroidectomy versus medical therapy are also still debated.\textsuperscript{40} Many patients experienced a decrease in their PTH levels to ≥70%, but not within the normal range. KDIGO suggests that PTH levels should be maintained between 2-9 times the normal upper limit. The optimal postoperative PTH level has not yet been determined.\textsuperscript{41} Symptoms, including severe bone pain and pruritus, have been shown to improve significantly after parathyroidectomy in patients with PTH >800 pg/ml.\textsuperscript{42} The risk of recurrent hospitalizations related to hypocalcemia was reported to be rare, at around 0.62%.\textsuperscript{31} The incidence of persistent (occurring within 6 months after surgery) and recurrent (occurring after >6 months post-surgery) SHPT is difficult to estimate as studies use varying threshold values. Some surgeons have proposed re-exploration in patients with PTH >800 pg/ml and hypercalcemia and/or hyperphosphatemia unresponsive to drug therapy.\textsuperscript{34,43} PTH should be measured at least every 6-12 months to identify recurrence.\textsuperscript{43}

Our patients also experienced an improvement in their anemia condition and a greatly reduced frequency of blood transfusions. Our report is consistent with some case reports before that anemia improved in patients with severe SHPT that underwent parathyroidectomy.\textsuperscript{44,45} Three patients still received routine EPO as needed, as before the surgery, but 1 patient no longer received EPO after the surgery. This indicates increasing EPO responsiveness, but this difference may also be influenced by other unevaluated causes of anemia, such as nutrition, bleeding, inflammation, etc. Potential mechanisms of anemia in SHPT were increased PTH may affect red blood cell production through direct toxicity on erythroid progenitor cells in the bone marrow and hemolysis, and indirect effects through induction of bone marrow fibrosis associated with osteitis fibrosa cystica. Bone biopsy data show that improvement in anemia after parathyroidectomy depends on the reversibility of bone marrow fibrosis.\textsuperscript{46} The relationship between post-parathyroidectomy SHPT and improvement of hypertension has been widely reported in the literature and several pathogenetic mechanisms have been described, such as decrease of vessel stiffness, improvement of contractile and chronotropic activity of myocardial cells, and decreased inflammation due to PTH-related atherosclerosis.\textsuperscript{37-38} Previous studies have shown a decrease in systolic and diastolic blood pressure in response to parathyroidectomy, and this beneficial effect is more evident in systolic blood pressure, supporting the hypothesis that changes in blood pressure after improvement in SHPT are related to a decrease in vessel stiffness.\textsuperscript{48-53}

As a case series study, this research has several limitations that must be considered. First, the study only presented four cases, which is a small sample size, and, therefore, may not be representative of the broader population of chronic HD patients with SHPT. Second, the study did not include a control group or compare the outcomes of parathyroidectomy with medical therapy, so it is difficult to conclude the efficacy of parathyroidectomy as a treatment option. Third, the study did not provide long-term follow-up data, so whether the patients experienced any adverse effects or recurrence of SHPT after the surgery is unclear. Lastly, the study was conducted in a single country and may not apply to other countries with different healthcare systems or patient populations.

**CONCLUSION**

Four ESKD patients undergoing dialysis who had severe refractory secondary hyperparathyroidism experienced total parathyroidectomy with autotransplantation have been reported. In our practice, parathyroidectomy achieved the desired biochemical goal and clinical improvement in a small number of patients undergoing the procedure. Although very limited, this case report could inspire larger prospective studies to evaluate the benefits of parathyroidectomy for increasing the quality of life of dialysis patients, especially in Indonesia, where drugs such as calcimimetics are still not widely available and expensive.

**CONFLICT OF INTEREST**

There is no competing interest regarding the manuscript.

**FUNDING**

This study received no funding.

**ETHICS CONSIDERATION**

This case study follows COPE and ICMJE protocols based on publication ethics guidelines. In addition, the informed consent for this study has been approved.
by the patients involved in this case series research.

**AUTHORS CONTRIBUTION**

APN has expertise in literature search, data acquisition, and manuscript preparation. They were responsible for conducting a thorough literature search, gathering data for the project, and preparing the initial manuscript. KT, on the other hand, contributed to the project's design and participated in clinical and experimental studies. They were involved in the data acquisition phase of the project, but did not participate in the data analysis or statistical analysis. A contributed to the definition of intellectual content and the manuscript editing and review. They did not participate in the project's data acquisition or statistical analysis.

**REFERENCES**


